Report of the Peer Review Panel on Photorefractive Keratectomy (PRK) Research

April 1998

American Institute of Biological Sciences
Scientific Peer Advisory and Review Services

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Contents

Executive Summary

In October 1997 the American Institute of Biological Sciences convened the Peer Review Panel on Photorefractive Keratectomy (PRK) Research. The panel conducted an independent review of the research literature concerning the procedure known as photorefractive keratectomy. The panel reviewed the available literature and

1. evaluated the quality and merit of the scientific and clinical data;
2. assessed the immediate and long-term outcomes of PRK;
3. related the information, as much as possible, to visual performance specific to military tasks;
4. outlined what is known and is not known about the procedure;
5. outlined knowledge gaps in the scientific and clinical literature; and
6. made recommendations for additional studies, some of which can be conducted only in the military setting.

PRK is a procedure that is gaining acceptance in the civilian population. It offers the myopic individual the hope, through a surgical procedure, to discard eyeglasses or contact lenses for distance vision with minimal risk. Its potential value to the military is to be able to correct the increased myopia of highly trained individuals who can no longer meet the uncorrected vision standards for a specific program, and thereby reducing training costs for replacement of personnel. Similarly, the potential to have an infantry or shipboard force that is independent of eyeglass and contact lens correction for better all-weather, all-conditions performance should be recognized. Other potential values are to prevent a reduction in the pool of potential recruits available for any military occupation that will occur with the increasingly widespread use of PRK in civilians and to increase the available pool of individuals for training for specific highly specialized military missions.

With these potential benefits in mind, a certain amount of caution must be exercised. Long term clinical data are not available. There are gaps in the knowledge of what happens in basic corneal wound healing. Refractive outcomes are not currently 100 percent predictable. Only two machines are currently approved by the Food and Drug Administration for clinical use. Modifications of the procedure are still occurring. The exact benefits and problems concerning military tasking are not known.

The panel encourages the U.S. Department of Defense (DoD) to proceed with well-planned studies of PRK within the military. This may be the only way to answer many of the questions concerning military-specific performance. No studies in the civilian population are available that relate specifically to military performance. Neither are such studies likely to be performed without DoD support, as they would have little meaning to most tasks required of nonmilitary populations in everyday life.

In the following sections, the panel summarizes the findings from the literature that it details in the body of the study, and repeats the specific recommendations for the use of PRK in the military and for additional studies to answer some of the questions that are military specific. As assigned in the Terms of Reference (Appendix B), the panel focussed its work on PRK rather than laser-assisted *in situ* keratomileusis (LASIK). Some information on LASIK is included, but a detailed literature review of LASIK would require another study. Although the four chapters of the study are attributed to individual authors or groups of authors, all members of the panel have reviewed the entire study and reached consensus on its contents.

CORNEAL AND OCULAR PHYSIOLOGY

Findings

Concerning the efficacy of PRK, the wound-healing responses in animal studies from rabbits and primates indicate that the PRK wounds heal predominantly by corneal fibrosis during the first 6 months after surgery. This leads to a complete regression of the refractive effect of PRK in test animals. Based on our knowledge of human healing patterns following radial keratotomy, we would suspect that healing following PRK is considerably delayed and may require up to 3 years to be initiated and perhaps 5 to 10 years or longer to be completed in some patients. While the physiologic effects of delayed wound healing are unknown, delayed healing in Radial Keratotomy has led to biomechanical weakening of the cornea and the development of hyperopic shifts in a subset of patients with a higher number of, and more centrally placed, incisions. Although a similar mechanical effect following PRK is not likely, due to the abrasive rather than incisional nature of the injury, the long term consequences of PRK and its effect on mechanical stability, corneal physiology and refractive stability remain a major concern that needs further study. Current clinical studies reporting results from 6-months and 1-year follow-ups are inadequate and do not assess the full potential of PRK to undergo considerable regression. In addition, clinical studies generally are performed on older individuals who are known to show less aggressive healing responses and undergo less regression. The military population at risk may be considerably younger, (i.e., in their twenties, and they should experience more exuberant healing and greater regression). Also, women of child-bearing age are at greater risk for regression during pregnancy, another concern for the military population.

Concerning the safety of PRK, incomplete regeneration of the epithelial basement membrane in animal studies is a major concern. The long-term effect of an abnormal basement membrane on epithelial and stromal differentiation and function is not known, and the potential risk for infection and epithelial erosion needs to be seriously considered. In addition, corneal wounds that remove the basement membrane heal by stromal fibrosis with deeper injuries, producing greater fibrosis. The presence of corneal fibrosis will clearly effect corneal transparency; the long-term clinical significance is not known. Furthermore, the safety of LASIK surgery is completely unknown.

Concerning predictability, differences in corneal hydration between patients make it unlikely that the accuracy of PRK correction can ever be much better than +1 diopter. Of course that does not take into account the effect of regression that is variable dependent on patient age, sex, and health.

Recommendations

The panel recommends that future studies sponsored by the DoD related to corneal and ocular physiology be directed toward answering the following three questions:

1. What is the cause of regression in patients—epithelial hyperplasia or fibrosis—and how long does it take to stabilize—5 years to 10 years?
2. What is the importance of an abnormal basement membrane? Is there any effect on long-term epithelial and keratocyte differentiation and functions, and what is the risk to later infection?
3. What is corneal haze, how can it be measured objectively and how does it correlate with visual outcomes including glare and low-contrast visual acuity?

Other recommendations for areas meriting further study are as follows (in order of their appearance in the Chapter 2):

1. What is the precise *in vivo* decrease in corneal thickness after PRK in patients, and how does achieved photoablation correlate with intended correction?
2. What is the risk for the development of early cataract following single and multiple PRK procedures?
3. What is the tolerance of the cornea to shear stresses after LASIK surgery?
4. What is the depth of injury to underlying cells—keratocytes and endothelial cells—in patients, and how does the depth of injury correlate with the development of haze and regression?
5. What is the risk of UV and solar radiation to haze and regression?
6. What is the effect of pregnancy and menopause on PRK?
7. Can growth factors or cytokines alter the post-PRK repair process?
8. What is the early inflammatory response and how does it correlate with haze and regression?
9. What is the mechanism of collagen fibrillogenesis and how does it relate to corneal haze?
10. What is the risk of corneal endothelial damage following LASIK?
11. What is the risk of corneal anesthesia following PRK, and how does reinnervation modulate epithelial healing and long-lasting epithelial defects after PRK? How does corneal anesthesia affect basal tear secretion and subsequent corneal drying and damage?

CLINICAL OPHTHALMOLOGY AND OPTOMETRY

Findings

Although PRK and LASIK are widely accepted and being performed worldwide, many controversies and gaps in knowledge exist with respect to safety, efficacy, and techniques. The following information summarizes the controversies and gaps in knowledge.

PRK versus LASIK

There is much more information on the results of PRK, both in terms of immediate results as well as longer-term follow-up (1–5 years) than LASIK. This gap in knowledge makes discussion of the relative value versus the risks of LASIK incomplete and somewhat speculative. Because of the likelihood of permanent nonattachment of the central corneal flap in LASIK, there may be dangers of flap loss secondary to trauma. LASIK may be superior to PRK for myopia greater than -7.0 diopters, however, and may be associated with more rapid recovery and visual rehabilitation with reduced central scarring. High myopia (greater than
-7.0 diopters) may also be better treated with PRK using second-generation solid-state lasers not currently approved in the United States. Exposure to UV light may have less effects on a patient after LASIK versus PRK.

Most studies have been relatively short term with PRK and limited with LASIK. There is a significant gap in knowledge with respect to potential long-term complications of both of these procedures.

Multizone versus Multiple Pass

There is controversy in the size of the optimal ablation treatment zone in PRK. Best optical results appear to be achieved using a 6-mm zone or larger in PRK in comparison with the previously smaller zones. The ablation zone in LASIK is small by necessity. Spot size appears to be related to "islands" of residual tissue in the ablation zone with large spot size more likely to cause these islands. Multiple pass techniques allow for "drying" and reduce islands. Multizone techniques allow for wider, shallower ablation zones with "smoother" shoulders that may have many positive benefits including reduced haze, reduced halos, better low-frequency contrast acuity, and less regression.

Low Energy versus High Energy

There may be a benefit in using low-energy techniques versus high-energy techniques, especially in higher myopia (less haze, less regression of the treatment effect). Low energy corresponds to solid-state and small-spot-size techniques. These will have more versatility in patient selection (hyperopia and all degrees of astigmatism) and adjustability with potential for computer-controlled, individually designed ablations to create the optimal corneal shape for every patient.

Epithelial Removal

There are several methods available to remove the corneal epithelium prior to PRK: mechanical (FDA approved), laser transepithelial ablation, alcohol debridement. Mechanical debridement of the epithelium with a brush is the most rapid technique but may be less complete than alcohol debridement. The significance of this is not well understood. Laser removal may stimulate less cytokine release from the unaffected edges leading to reduced apoptosis and scarring.

Epithelial Healing

There is little data to support the safety and efficacy of contact lenses in treating epithelial defects. Current practice includes contact lens wear to reduce pain, but is recognized to prolong the epithelial defect for approximately 1 day. In addition, ocular surface diseases such as rosacea, tear dysfunction, and obstructive meibomitis are known to retard healing and should be treated prior to PRK. Use of cytokines to retard apoptosis or to stimulate epithelial growth may prove beneficial.

Contact Lens Wear

Because PRK does not alter the peripheral corneal curvature (unlike RK which flattens it), patients can resume contact lens wear if required. There are no reported problems in the ability to wear contact lenses successfully after PRK, if needed.

Steroid Use After PRK

The use of topically applied corticosteroids following PRK is controversial because of potential complications such as steroid-induced glaucoma, cataracts, and herpes simplex infection. Currently, topical steroids are commonly used in the United States, but not by some European surgeons. More information is necessary to determine the optimum approach.

Spatial Contrast Sensitivity

The loss of low spatial contrast sensitivity following PRK during the first postoperative year is well described in the literature. There are no data that adequately address the issue of whether or not this is relevant to performance or is predictive of decreased visual function.

Performance Standards Pre- and Post Operative

It is critical to know how the performance of an individual is affected by PRK with respect to specific military duties. Pre- and postoperative tests need to be developed to assess the impact on specific areas such as nightdriving, pilot function, rifle performance, and SEAL performance.

Recommendations

The panel recommends that future studies sponsored by the DoD related to clinical ophthalmology and optometry and PRK address the following three research requirements:

1. What is the residual need for glasses or contact lenses following PRK or LASIK? (research requirement 3-1)
2. What is the impact of reduced low-contrast and night vision acuity following PRK or LASIK and how long does it persist? A particularly relevant area for research involves the effects of PRK and LASIK on night driving. Actual driving simulators with a control group may be best to make this assessment because devices that simulate only the visual experience in a narrow view forward (such as the mesoptometer) may be inadequate to assess the entire dynamic visual field. (research requirements 3-5 and 3-10)
3. What is the effect of hypo/hyperbaric environments on LASIK? (research requirement 3-7)

Other recommendations for areas meriting further study are as follows (in order of their appearance in Chapter 3):

1. What are the best measures of visual performance for military tasks (what should the performance standards be for specific tasks for groups such as SEALs, special forces, pilots) since high-contrast Snellen acuity, the typical standard, does not describe the extremes of visual demand? (research requirement 3-2)
2. How long does it take to recover usable vision following PRK or LASIK? (How long would a member be off duty following PRK?) (research requirement 3-3)

3. How long does it take to recover to best spectacle-corrected visual acuity (BSCVA) or best uncorrected visual acuity (UCVA) following PRK or LASIK? (research requirement 3-4)

4. What is the pattern of return to adequate resistance to lateral (shear) forces with healing following LASIK? (Would the flap withstand wind shear as with parachuting or blast forces?) (research requirement 3-6)

5. What has been the positive and negative experience of police and fire-fighting agencies that have authorized PRK or LASIK? (research requirement 3-8)

6. How many patients with BSCVA of 20/20 before PRK or LASIK have 20/25 or worse BSCVA following PRK or LASIK? (research requirement 3-9)

7. How long does the refraction remain stable? Is there a difference in stability between PRK and LASIK? (research requirement 3-11)

8. What should the standard analysis be for determining the effectiveness of astigmatic surgery? (research requirement 3-12)

PRK AND VISUAL FUNCTION

Findings

A summary of the panel's findings on PRK and visual function are listed below, by category.

Overcorrection and Undercorrection

Virtually all studies of refractive stability following the PRK procedure show a common pattern of post-PRK refractive error. The refractive error immediately following PRK is usually hyperopic (overcorrection), but during the first 2 or 3 months, the manifest refraction gradually becomes less hyperopic (more myopic) again.   In some cases, this myopic regression results in emmetropia, but in others, it leaves the patient hyperopic. In most studies, the final Rx after regression has reverted to myopia. In most studies, the refractive error stabilizes after about 3 months, but this finding is not universally observed, and some studies report continuing regression in high myopes over a 1-year period.

From the literature, it appears that success rates are improving: Final post PRK Rx's are getting closer (on average) to emmetropia.

Because ablation depth will vary with corneal hydration and healing processes, and because both can vary between eyes, it is unlikely that the standard deviations in achieved Rx will be able to be reduced to zero in the same way that the mean Rx can be refined.

Results to date seem to indicate that large initial overcorrections, large myopic regressions, and large residual myopias can be avoided by using a larger ablation zone. We have not found any reasonable explanation for why larger ablation zones should produce improved refractive outcomes.

Stability of the post-PRK refraction has been studied under high-altitude conditions known to produce large hyperopic shifts in post-RK eyes. Unlike post-RK eyes, no hyperopic shifts were observed in the PRK eyes during a 3-day exposure to a hypobaric environment.

Use of large (6-mm) ablation zones seems to correct some serious problems with earlier data collected with 4-mm ablation zones, and post-PRK refractions are stable and close to emmetropia.

Reliance on direct corneal measurement should be utilized to see if the procedure actually changes the cornea by the desired amount because post-PRK Rx is an indirect measure that can be influenced by pupil size.

Changing the Shape of the Cornea

Post-PRK eyes do experience halos when the pupil dilates at low light levels (78 percent in the early postoperative period).

The dioptric step introduced into the peripheral optics makes the eye more myopic at the pupil margin (outside of ablation zone) than at the pupil center (within the ablation zone). This bifocal nature of the post PRK cornea is also likely to be present in a post-LASIK cornea.

Topographical studies report myopic "islands" in the center of the ablation zone, which may be absent with newer lasers. It is not clear what produced them or why they generally disappeared after 3 months.

Corneal Transparency

The ablation process causes the usually very transparent corneal stroma and corneal epithelium to lose some of its transparency. This transparency loss peaks during the first month(s) and declines possibly back to normal levels at 3+ months. The method for removing the epithelium prior to the stromal ablation may also influence the amount of transparency loss. The biological causes need to be clearly identified before a rational approach to eliminating them can be initiated.

The glare effects peak early in the post-operative period (2–3 months, and are virtually absent at 1 year in most eyes). However, there are persistent glare and haze problems that linger in some eyes. Currently there is no clear hypothesis to explain why some eyes have persistent haze.

Night Vision

The change in pupil size and the changes in the visual stimulus can have significant interactions with the optical effects of PRK. Large pupils will include the edge of the ablated zone. The edge of the ablated zone includes (1) increased haze (according to one study) and (2) a huge dioptric step (equal to the step between post-PRK Rx and pre-PRK Rx) that creates a bifocal visual system with decreased image quality and noticeable annular blur rings (halos) around bright light sources. Reduced light levels lead to reduced signal-to-noise ratios and reduced visual contrast sensitivity (and resolution). Thus any additional reductions in contrast sensitivity caused by PRK may have added impact at night where more targets are already close to contrast threshold.

In combining the two effects (pupil dilation and the accompanying reduction in image quality) with the inherently larger impact PRK will have on low-light vision, it is

reasonable to expect that the impacts of PRK on vision will be maximal at night. The presence of bright light sources in the nocturnal environment will have an additional detrimental effect on any eye with a scatter source such as the subepithelial losses of transparency present in all eyes during the 1–3-month post-operative period after PRK.

One study reported large reductions in low-contrast acuity in the presence of glare, problems with halos (100 percent post-PRK surgery, and 45 percent at 1 year), increased glare sensitivity that was still present in 66 percent at 1 year, and 19 of 26 patients would have failed the German night driving test based on these results and thus would not be licensed to drive at night in Germany. It is worth noting that studies of night driving point out that high-contrast visual acuity measurements taken at high light levels overestimate visual performance under night driving conditions.

Vision with Imaging Systems

Imaging systems such as image intensification devices (e.g., night vision goggles) pose a special problem for PRK. These devices are designed to multiply the photons from a nighttime scene. In doing so they amplify an inherently noisy signal (reducing the light level is equivalent to reducing the signal-to-noise ratio because of the Poisson nature of photon distributions) and the amplification process adds its own noise. This reduced signal-to-noise ratio is compounded when the object has a low-contrast target (such as a sand dune in the desert) because a low-contrast object also has a low signal to noise ratio. These three factors (low light level, image intensification, and low contrast) already render some objects invisible that we might expect to see because of the high mean intensity of the night vision goggles. Any additional reduction in the signal-to-noise ratio in these marginal conditions could render even more stimuli invisible. It is therefore possible that a PRK procedure that allows high-contrast objects viewed in daylight to be seen with ease may render many low-contrast objects invisible when viewed with night vision goggles.

Recommendations

The panel's most important recommendations related to PRK and visual function are summarized below.

1. The most daunting, yet most critical task in assessing the consequences of PRK for military operations is the design and implementation of appropriate performance tests. We note that many critical military operations are conducted under extreme conditions in which the visual system's ability to pick up the required information is pressed to a variety of limits. We recommend that performance tests be designed and conducted that require subjects to perform representative tasks under visual conditions that mimic those in the specific military situations concerned. It would be best to conduct such tests using within-subject designs so that the same subjects can be tested in the same tasks with different simulated optical degradations. The more important results should ultimately be confirmed with PRK subjects and controls.

2. Given the military needs for optimal night performance, and the paucity of data (one abstract from the Association for Research in Vision and Opthamology) on night vision with PRK, an obvious gap in the experimental literature exists. There is a desperate need for good psychophysical data and controlled experiments on the effects of PRK on night vision with and without amplification.

3. We strongly recommend that any future PRK studies evaluate visual function using measures other than high-contrast letter acuity when assessing the suitability of PRK for the military and that those measures be tailored to the specific military task in question. Some aspects of the viewing situation are particularly important to measure

and examine in the research effort. These include the luminance, contrast, and spatial frequency content of the targets; the subject's pupil diameter; and the position and intensity of glare sources.

4. Considering the inconsistencies in the literature and the inadequate level of optical data on PRK, we recommend a single study that monitors (1) Rx, (2) corneal thickness changes, and (3) corneal curvature changes. Using a simple model, these data can confirm the success or failure of PRK in achieving what it is supposed to achieve. We can find no study that has formally tested the refractive effects of PRK in this way.

5. Future studies should employ better optical methods (compared with inferred optical changes based on indirect measures used with normal eyes), including proper assessment of contrast sensitivity before and after PRK. We suggest that the military consider simulating the optical degradations associated with PRK as another possible method for evaluating the impact of PRK on visual function.

1

Introduction

John E. Sutphin

At the request of the U.S. Army Medical Research and Materiel Command (USAMRMC), in October 1997 the American Institute of Biological Sciences convened the Peer Review Panel on Photorefractive Keratectomy (PRK) Research. The panel was convened to provide an independent peer review of the available literature to the U.S. Special Operations Command, the USAMRMC, and the U.S. Navy Medical Research and Development Command. The panel was asked to evaluate the scientific and clinical data relating to PRK and, from that evaluation, to assess the near- and long-term outcomes of PRK and relate this information to visual performance tasks specific to the military in conditions that are likely to be encountered in military operations or with unique military equipment. Background briefings were provided by the Navy, the Army, and the Air Force to give the panel a framework for the military's interest in PRK and its potential military applicability. The Terms of Reference for the panel is provided in Appendix B.

The military has long recognized the shortcomings of standard optical devices (glasses and contact lenses) to correct ametropia. Elaborate systems are in place to provide service members with refractive error correction upon enlistment and throughout their career in every conceivable venue to prevent members from becoming casualties simply by losing their glasses. Many items of equipment, such as gas masks, have to be designed to allow for different refractive errors. In some situations, the military has reduced the problem by restricting certain occupations to members that meet minimal standards of uncorrected visual acuity or refractive error. In some situations, the military has authorized and provided contact lenses to enhance military performance (submariners, helicopter and other pilots with contact lenses) and more recently has begun investigating the possibility of refractive surgery to enhance military performance (Schallhorn et al., 1996). In addition, with the changes in refractive error that come with time, highly trained service members are becoming nonqualified based on their refractive error, and refractive surgery may be a way to retain these members in their specific military jobs. The military also recognizes that with the increasing availability of PRK and its related procedure, laser-assisted *in situ* keratomileusis (LASIK)—both now being performed worldwide and approved since 1996 in the United States—the civilian pool for new recruits will be reduced if PRK and LASIK remain a disqualification for service. The total number of people with PRK was estimated at 50,000 in 1996 and will probably exceed 75,000 in 1997 with an additional 50,000 LASIK patients. A second survey estimates that 94,500 laser procedures were done in 1996 with 22 percent LASIK and approximately 200,000 in 1997 with 29 percent LASIK (*Ocular Surgery News*, January 1, 1998, p 16). These numbers are projected to rise to a total of 500,000 procedures (about 85 percent LASIK) per year by 2000 in the United States alone (Chynn, 1997). These people are presently excluded from military service, but with the reducing pool of potential volunteers they could be considered for acceptance into the military. If PRK and LASIK are successful, the limitation of refractive error in the civilian pool of potential recruits could be reduced.

The advent of radial keratotomy in the 1970s and 1980s led to widespread interest among young service members and civilians. However, the military experience with radial keratotomy was limited and mostly characterized by the complications and side effects of that procedure. Complications that included daily variability of vision, glare and halos, inaccuracy, and ultimately long-term progression were of concern. Eventually the military demonstrated the decidedly adverse effect of altitude on radial keratotomy patients, even after a year of healing (Mader, 1996). This experience has led to caution in the introduction and acceptance of PRK for myopia. This panel review is to both define what is known about PRK in 1997 but also to anticipate what may become known in the next 10 years.

Unlike radial keratotomy in which widespread application occurred quickly and the procedure required only readily available equipment, the limited number of excimer lasers has reduced basic science research regarding PRK. Nevertheless, over 1,000 references have been identified and over 250 have been reviewed specifically by this panel. In general, peer-reviewed data will lag clinical experience by 2–3 years, and much of the data used for determining Food and Drug Administration (FDA) approval are never published in the format submitted.

At this time there are only two lasers that have been approved in the United States by the FDA for performing PRK (the VISX Star and the Summit Apex). The VISX laser is approved for patients 18 years of age or over with refractive error from -1.00 to -6.00 diopters of sphere and for 21 years or older with -0.75 to -4.00 diopters of cylinder using a 6.0-mm ablation zone. The Summit laser is approved for patients 21 years of age or older with refractive error from -1.50 to -7.00 diopters of sphere using a 6.0-mm ablation zone. Data of other lasers have been submitted to the FDA, and the panel has seen the Autonomous Technologies Corporation data submitted to the FDA for the range from -1.00 to -10.00 diopter sphere and -0.50 to -6.00 diopters of cylinder. There was no age limit provided and the ablation-zone diameter was 6.0 mm for the sphere and 5.5 x 7.5 mm for the cylinder. Because this laser is not approved, we have included only minimal information from it. A review of the current requirements among the three services (Walsh and Levine, 1987; US Air Force, 1994; US Army, 1995; US Navy, 1991) suggests that people with up to -8.00 diopters of cylinder and sphere could qualify for some military positions. Data have been submitted to the FDA by VISX to extend the range of PRK to -10.00, but the data were not made available to the panel. Therefore, we emphasize the studies with up to -8.00 diopters of treatment corresponding to the military needs as we interpret them. However, most military members are in the range of low myopia (Schallhorn et al., 1996). Therefore, current equipment should be adequate for treating the vast majority of military members.

In Chapter 2, "Corneal and Ocular Physiology," we address what is known about the mechanism of action of the lasers and the resulting alterations in the corneas of animal models and humans. The difference between wound healing in animals and humans is emphasized, pointing out the paucity of good information about wound healing in humans and the lack of healing compared with rabbits and primates in particular.

In Chapter 3, "Clinical Ophthalmology and Optometry," we review the clinical results and duration of effect as they are presently known. Specific questions of eligibility, efficacy, short- and long-term safety, job performance requirements and limitations, reoperation success, current technology, and treatment techniques are addressed.

In Chapter 4, "PRK and Visual Function," we review the optics of PRK and the measurement of visual performance following PRK. Emphasis is placed on the lack of scientific data relating visual acuity and contrast sensitivity testing to various tasks, including walking, sports performance, reading, driving, and flying. At present, high-contrast visual acuity is the only standard used by the military, and PRK results in acceptable levels; however, the concern is for visual performance in low light level or

low-contrast settings that are specifically vulnerable and may be better predictors for some military tasks (detecting targets at night, in fog, etc.).

PRK in clinical ophthalmology and optometry is an evolving procedure. There is a rapid growth in the frequency of PRK, especially when it is performed under a flap (e.g., LASIK), that is attributed to its clinical appeal for both physician and patient. However, there is even less information available about wound healing, clinical results, and visual performance following LASIK. Despite the absence of a thorough understanding of the physiology and optics of PRK, it has become the best characterized and most widely applied of the current refractive procedures. PRK is successful in reducing myopia and achieving uncorrected vision to a driving standard (20/40). The safety and efficacy of FDA-approved lasers are reasonable, but are expected to improve with newer technologies under development. Permanent sight-threatening complications occur in less than 1 percent of patients and severe vision loss in less than 0.2 percent.

In the following three chapters, the panel identifies areas requiring additional research that should help illuminate the specific military applicability of PRK.

2

Corneal and Ocular Physiology

James V. Jester,
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INTRODUCTION

Considerable research has been conducted on evaluating the effects of excimer laser photorefractive keratectomy (PRK) on corneal physiology and function in both clinical and experimental settings. About 200 papers covering ocular biomechanics, histology, immunohistochemistry, ultrastructure, and physiological and clinical testing have been published since the PRK procedure was introduced. From this body of work, an understanding of how PRK affects corneal structure and function and how the corneal response in turn affects PRK outcome has begun to be established. Major areas that we address in this chapter are as follows: excimer laser interactions with the cornea; general wound-healing responses; tear film, cytokines, growth factors, and hormones; corneal Epithelium; corneal stroma; and corneal endothelium. Each of these technical areas impacts, directly on our knowledge of the safety, efficacy, and predictability of PRK and its ultimate use as a surgical procedure for the correction of corneal refractive errors. Of specific interest is the identification of changes to and responses of the cornea that may lead to secondary effects that would influence the safety, efficacy, and predictability of PRK. We conclude the chapter with a summary and recommendations.

EXCIMER LASER INTERACTION WITH THE CORNEA

Trokel (et al. 1983) and Puliafito (et al. 1985) were the first to demonstrate precise etching of the cornea using 193-nm high-powered UV radiation from the excimer laser. At the right power, excimer radiation produces "ablative photodecomposition" of organic polypeptides by breaking molecular bonds and producing smaller volatile fragments through direct photochemical interaction without heating the adjacent tissue. Studies have shown that the fluency thresholds above 40 mJ/cm^2 lead to photoablation of the corneal tissue (Kermani et al., 1988), leaving adjacent tissue completely intact except for a 0.2-mm-thick, electron-dense surface condensation (Puliafito et al., 1987) referred to as a pseudomembrane. There are several concerns with using the excimer laser to photoablate the corneal surface, including (1) variation in photoablation rates, (2) uv radiation effects, (3) thermal effects, and (4) biomechanical effects.

Variation in Photoablation Rates

Excimer laser corneal tissue ablation rates have been measured by deep stromal ablation or corneal perforation and shown to be approximately 0.5 μm of tissue photoablation per pulse (Krueger and Trokel, 1985; Srinivasan et al., 1987). However, clinical application using this rate has produced considerable undercorrection that has been thought to be associated with regression and wound healing following surgery. More recent *in vivo* measurements using Scheimpflug videography suggest that the nominal photoablation rate may be significantly less, closer to 0.27 μm/pulse (Huebscher et al., 1996). The discrepancy between the experimental and nominal rate could be multifactorial and due in part to differences in the photoablation rates, corneal hydration and dehydration, as well as wound healing.

Deeper photoablations have been shown to have rougher surface profiles by scanning electron microscopy, suggesting differences in the photoablative properties between anterior and posterior corneal layers (Taylor et al., 1994). Tissue hydration has been shown clearly to be important in several studies from different laboratories. Fields et al. (1994) have shown that edema of the corneal tissue leads to rougher surface photoablations suggesting a change in the tissue ablation rate when corneas are hydrated. More quantitative data have been provided by Dougherty et al. (1994) who has measured the tissue hydration effects on the removal of dry tissue mass from the cornea during PRK. Dougherty's data indicate that dehydrated or deturgesed tissues show a greater dry tissue mass removed than wet or edematous tissues leading to a greater rate of photoablation and potentially overcorrection for dry compared with edematous corneas. This effect of dehydration is consistent with the effect of blowing dry nitrogen gas over the ocular surface during PRK, which results in rougher corneal surfaces (Campos et al., 1992b) and less-predictable effects (Gilbert and Meltzer, 1992).

Recent quantitative studies using *in vivo* confocal microscopy questioned the earlier results with Scheimpflug microscopy that show a difference in the nominal and experimental photoablation rates. Maximal corneal thinning following PRK in rabbits as measured by *in vivo* confocal microscopy showed on average a photoablation rate of 0.5 μm/pulse (Moller-Pedersen et al., in press), which is in agreement with the experimental rates. This observation also questions the effects of hydration and dehydration, at least for the rabbit model in which the surgeon, time of surgery, and methods can all be held constant. It should be noted, however, that although on average the rate of photoablation in the rabbit is 0.5 μm per pulse, the range in achieved photoablation depths is considerable, 112–130 μm for a predicted 118 μm. This variation suggests some tissue variability that might result in at least 1–2 diopters of under- or overcorrection. In additional this variability may be even greater in patients where the achieved depth of photoablation shows an even greater variation when measured using these *in vivo* confocal techniques (Moller-Pedersen et al., 1997). From these studies, it is clear that many factors can influence the actual ablation rate and achieved photoablation depths in any single patient. Until the sources of these variations are known and can be accurately accounted for, it will be difficult to predict precisely what the actual photoablation and immediate correction will be. The panel recommends that further study of photoablation rates be conducted in patients by accurately and precisely measuring corneal thinning after PRK using similar techniques as those used by Moller-Pedersen (1997, in press).

UV Radiation Effects

Of some early concern with the use of 193-nm excitation was the potential mutagenicity and carcinogenicity of the irradiating light (Schein, 1992). UV irradiation can cause DNA damage in *in vitro* tests, though 193 nm produces less damage than 243

or 308 nm. Although not directly investigated in any experimental studies involving the cornea, the potential for excimer radiation to cause these problems is not likely given that primary corneal tumors are exceedingly rare, suggesting resistance of the cornea to malignant transformation. Furthermore, animal models of UV-induced tumors require prolonged and repeated exposures for tumor induction. Such exposures are beyond that received by excimer PRK.

Excimer radiation does appear to produce oxidative damage to proteins in the aqueous chamber and lens suggestive of cataractogenesis. In reports from Italy, Costagliola and colleagues have shown that 193-nm scanning excimer (Meditech Aeschulap laser) exposure to the cornea during PRK produces an immediate dose-dependent change in the levels of reduced and oxidized glutathione in the rabbit (Costagliola et al., 1994). The exposure levels tested ranged from 6 diopters of correction or 3,065 pulses to 24 diopters or 12,757 pulses at 20 Hz with a fluence of 250 mJ/cm^2. All treatment groups showed significant decreases in glutathione levels with concomitant increases in glutathione-oxidized levels. In a later study, animals treated with 6,032 pulses (12.0 diopters) showed persistent effects in the lens with suppressed glutathione and elevated glutathione-oxidized levels remaining significantly changed for 4 weeks after surgery (Costagliola et al., 1996). It is not known if these effects in the rabbit are predictive of humans or primates. This work has not been duplicated or substantiated, and its relevance to increased risk of cataract in patients is not known. There has been no report on the development of cataract after excimer PRK. Clearly, further work is necessary to rule out this potential, long-term side effect. The panel recommends that any large clinical study that is conducted should consider cataract outcomes as an aim of the project.

Thermal Effects

As noted above, 193-nm photoablation of tissue is thought to occur without significant thermal heating (Puliafito et al., 1985); however, as described by Puliafito, there is a thin zone of denatured material, 0.2 µm thick, that is deposited along the surface of the photoablated tissue, the origin of which is not known. In measuring the thermal changes along linear excimer photoablations, Berns et al. (1987) have shown that the surface temperature along an incision may increase by as much as 20°C from a surface temperature of 18.4°C. This increase is much higher immediately after or at the time of the laser pulse, reaching as high as 53°C in the region of the laser plume. Increased corneal surface temperature of 10–12°C has also been noted by Niizuma et al. (1994) in rabbit and pig eyes with 1,000–500 pulses. A similar increase has been demonstrated more recently by Betney et al. (1997) using ocular thermography during PRK on myopic patients.

In general it appears that tissue immediately adjacent to the excimer photoablation may increase in temperature to around 40°C. As proposed by Niizuma et al., elevation of the corneal stromal temperature to this level may be responsible for denaturation of adjacent collagen tissue and explain, in part, pseudomembrane formation, decreased corneal clarity, and the development of haze following PRK. An old report in the literature suggests that 50 percent of corneal collagen may become denatured at 38.7°C, completely denatured at 40°C with severe molecular alteration seen at 50°C (Lewis et al., 1967). Based on these findings, Tsubota et al. (1993) have proposed the use of cooling the cornea prior to PRK surgery to prevent undue thermal heating. In an anecdotal report of three cases, Tsubota suggests that cooling of the cornea may decrease postoperative haze. The clinical significance of these findings has yet to be substantiated. It is also difficult to understand how the corneal stroma would become denatured at temperatures so close to normal body temperature, i.e., 37°C.

However, thermal heating may be greater immediately adjacent to the wound than has yet to be measured.

Biomechanical Effects

As currently practiced, PRK does not appear to significantly alter any biomechanical property of the cornea. Any compromise in ocular integrity or increased risk of rupture requires photoablation in excess of 80 percent of the corneal thickness, or equivalent to over 42 diopters of correction (Burnstein et al., 1995). This is substantially beyond the level of correction achievable with PRK. PRK may have a slight effect on the measurement of intraocular pressure (IOP). In a retrospective study of 1,320 patients receiving PRK, there was a significant drop in IOP from 2 to 5 mmHg that directly correlated with the achieved change in refraction from -1.0 to -9.5 diopters (Chatterjee et al., 1997). A similar effect was not detected in rabbits 2.5 to 3 months after 5- and 15-diopter correction (Tuunanen et al., 1996). The inability to detect any change in rabbits may be related to differences between humans and rabbits regarding the corneal mechanical properties and wound-healing response. Rabbits show 80 percent regrowth of ablated tissue by 3 to 4 months after PRK (Moller-Pedersen et al., in press). Furthermore, tensile and intralamellar adhesive strength are significantly different between humans and rabbits.

In contrast to PRK, LASIK may achieve depths that could severely compromise the cornea to blunt trauma; however, in one report there appeared to be no difference in the effect of LASIK and PRK on the biomechanical stability of the cornea (Peacock et al., 1997). Also, little or nothing is known about the integrity of the corneal flap and whether healing after LASIK ever restores the ability of the anterior cornea to withstand sheer stress, particularly those types of stresses that might be encountered by military personnel. The panel recommends that further study of the sheer stress be conducted on LASIK to establish the tolerance of LASIK flaps to withstand lateral force. These studies, if conducted in animals, must be interpreted cautiously because animals show considerably greater healing responses than humans that may restore some intralamellar adhesive strength, which may not occur in patients.

GENERAL WOUND-HEALING RESPONSES

It is widely recognized that a major criterion that is important to the successful application of excimer laser-based PRK is that the tissue healing processes must maintain normal corneal transparency and not significantly distort the induced refractive correction by the addition of new corneal tissue, or, if so, that the addition of tissue is predictable. To understand the effect of wound healing on PRK, corneal repair has been evaluated extensively using conventional histopathologic and ultrastructural techniques in both animal models: primates (Fantes et al., 1990; Hanna et al., 1990, 1992; Marshall et al., 1988) and rabbits (Tuft et al., 1989), and in human pathologic tissue samples (Fagerholm et al., 1994). It must be remembered that photoablation removes or damages (1) the central corneal epithelium and underlying epithelial basement membrane, (2) adjacent corneal keratocytes, and (3) corneal stroma. In general, the histopathologic studies show that photoablation results initially in the directed migration toward the wound of activated epithelial cells, fibroblasts, and macrophages which participate in the removal of damaged tissue, the replacement of epithelial cells and keratocytes, and the *de novo* synthesis of new basement and stromal extracellular material or matrix. Below is presented the major histologic findings covering these areas.

Histological Findings

Epithelium

For the most part studies show a rapid epithelial wound-healing response with resurfacing of the photoablated corneal surface within 2–7 days depending on the size of injury. These rates are between those observed for simple scrape injuries, which leave the basement membrane intact and heal in 2–3 days, and manual lamellar keratectomy wounds, which remove the anterior cornea by blunt dissection and require 7–8 days to resurface (Essepian et al., 1990). Complete establishment of a normal corneal epithelial surface, however, requires the formation of both a new epithelial basement membrane (originally removed by photoablation) and hemidesmosomal cell-matrix attachment sites required for firm epithelial cell attachment. Studies in primates indicate that attempts to reform the epithelial basement membrane may occur as early as 7 days after injury with focal areas of basement membrane distinguishable by transmission electron microscopy (Fantes et al., 1990) and immunochemical detection of basement membrane matrix, type VII collagen (SundarRaj et al., 1990). However, long-term ultrastructural studies indicate that the basement membrane is abnormal and not completely reformed by 18 months after surgery in primates (Hanna et al., 1990), raising concern as to whether a normal basement membrane is ever re-established.   In additional, several histologic studies have reported an apparent increase in the epithelial thickness or hyperplasia following PRK measuring up to 12 cells and 80 μm thick in primate eyes receiving 7.0-mm-diameter ablation (Hanna et al., 1992). A similar observation has been made by Fagerholm et al. (1994) from human samples. Although the validity of these observations on fixed and processed tissue remain questionable, clinical opinions support a role for epithelial hyperplasia in explaining the regression of refractive effect following PRK. This association is discussed more fully below (see Regression on page 2-12). Finally, more-detailed cellular and molecular studies have been also performed on the tear film and epithelial function that are reviewed and discussed below in the sections, "Tear Film, Growth Factors, Cytokines, and Hormones" and "Corneal Epithelium."

Adjacent Keratocyte Death

Histologic studies of primate corneas have shown that immediately after surgery there is a marked reduction in the number of keratocytes in the anterior 40 μm of the stroma suggesting keratocyte cell death (Fantes et al., 1990). Keratocyte death following PRK has also been demonstrated in the rabbit using light and transmission electron microscopy (Hanna et al., 1989) as well as by *in vivo* confocal microscopy (Chew et al., 1995). Keratocyte death can be attributed to thermal or mechanical damage because photoablation increases the local corneal temperature by 10–20ºC (Berns et al., 1987; Betney et al., 1997; Tsubota et al., 1993) and generates an acoustic shock wave of about 80 atm (Kermani and Lubatschowski, 1991).   However, death of anterior stromal keratocytes can also be induced by simple epithelial denudation as first biochemically recognized in 1962 by Herrmann and Lebeau (1962) and later histologically verified by Dohlman et al. (1968). These findings suggest that the reaction may not be specifically related to photoablation but may be related to osmotic changes (Campos et al., 1994; Nakayaasu, 1988) or mediated by cytokines released by trauma to the epithelium and the putative induction of keratocyte apoptosis (Wilson et al., 1996a,b).   The exact mechanism(s) underlying post-PRK anterior stromal keratocyte death remains to be fully elucidated and are discussed more completely below (see section "Corneal Epithelium").

Virtually nothing is known about the early changes following PRK in the human population with regard to the depth and extent of keratocyte injury, if any. Following LASIK, depth of injury may have more severe consequences where injuries may extend to the corneal endothelium. With the recent advances in microscopy these studies could be conducted to establish the extent of injury for patients. The panel recommends that clinical studies should be conducted to evaluate acute depth of injury and establish both the presence and the extent of risk to underlying cells, keratocytes, and endothelial cells.

Stromal Repair

Because the earliest histologic samples evaluated thus far in primates are 7 days or later, very little is known about the initial response and later activation of stromal keratocytes following PRK. Based on wound-healing studies from other systems, it is presumed that cells become activated and then proliferate and migrate toward the wound during the first week after injury. At 7 days there is an increase in the number of keratocytes adjacent to the wound that dramatically increases over the next 3 weeks (Fantes et al., 1990). Cells within this region appear fibroblastic with extensive rough endoplasmic reticulum indicating active synthesis of new extracellular matrix. This region also exhibits extensive vacuolation adjacent to the epithelium and within the anterior stroma. The origin of the vacuoles, whether extracellular or intracellular, are not clear nor is the relevance to wound healing. Interestingly, it is at this phase of the wound-healing response in which the greatest degree of clinically observable haze is detected in primates (Fantes et al., 1990), suggesting that haze may be associated with either the dramatic increase in numbers of fibroblastic cells or the deposition of new extracellular matrix. Over time, there is a decrease in the number of fibroblasts within the wound area progressing toward normal by 9 months (Fantes et al., 1990), but remaining slightly increased in number and activity to 18 months (Hanna et al., 1990). The amount of new extracellular matrix or fibrotic tissue that is deposited during wound healing has been evaluated in rabbit corneas by staining the wound bed immediately after surgery with the fluorescent compound dichlorotriazinyl aminofluorescein (DTAF) that covalently binds to the host stroma and serves as a marker of the original corneal tissue. Using this technique, Tuft et al. (1989) have shown that there is virtually no difference between the amount of new fibrotic matrix deposited after PRK compared to lamellar keratectomy wounds in the rabbit. Even more important, immunohistochemical studies in primate corneas show no difference in the types and distribution of extracellular matrix proteins (collagen type VII, III, VI, keratan sulfate, fibrinogen, fibronectin, and laminin) that are deposited between PRK and manual keratectomy (Malley et al., 1990; SundarRaj et al., 1990). Overall, it is apparent that PRK produces very similar wound healing responses to that observed following manual lamellar keratectomy which is known to produce fibrotic tissue. Additional studies examining the specific cellular and molecular response of the stroma to PRK are reviewed and discussed in the section "Corneal Stroma."

Summary

In general, corneal wound repair is a complex, multifactorial process for which many of the cellular and molecular mechanisms controlling the wound healing process are either not known or are only poorly understood. These cellular and molecular events involve responses from the entire ocular surface and cornea and are reviewed and discussed separately in the following sections of this chapter. For the most part this work has been carried out on various *in vitro* and animal models. Very little is known concerning the specific cellular and molecular responses of the human cornea to excimer

PRK surgery and how these responses influence the safety, efficacy, and predictability of PRK. Through clinical studies in humans two major complications of PRK have been identified—haze and regression—and the responses of the tears, epithelium, stroma, and endothelium have all been implicated in participating or contributing to these complications. In the following sections we provide a review of these complications and how they relate to the general wound-healing response.

Haze

The term haze is a general term used to describe the transparent, optical qualities of the cornea following PRK. Hence, it is a clinical term with an unclear physiological and optical basis. This term has been used consistently in the literature to describe the development of opacity following PRK in both animal models and patients. The actual measurement of haze as routinely performed clinically involves the subjective determination by clinicians of the degree of opacification of the cornea as compared with "standard" reference slit-lamp photographs. A generally accepted clinical grading system has been devised that categorizes haze into the following grades: grade 0, totally clear; grade 0.5, a trace or faint corneal opacity seen only by indirect broad tangential illumination; grade 1, opacity of minimal density seen with difficulty with direct and diffuse illumination; grade 2, a mild opacity easily visible with direct focal slit illumination; grade 3, a moderately dense opacity that partially obscures the iris details; and grade 4, a severely dense opacity that obscures completely the details of intraocular structures [original description by Fantes et al. (1990)]. Such a system is highly subjective, and the repeatability and reproducibility are not well established. Furthermore, a subjective grading system is of limited use in investigating the relationship between changes in corneal transparency and the cellular and molecular mechanisms involved in the development of haze.

Various attempts to objectively measure haze have been proposed, including Scheimpflug photography (Binder et al., 1996), quantification of image intensity from slit-lamp photomicrographs with (Maldonado et al., 1996, 1997) and without (Chang et al., 1996a) digital image processing, and scatterometry using image intensity measurements with (Lohmann et al., 1991) and without (Braunstein et al., 1996) a polarizing light source. Most of these techniques have yet to be tested in experimental settings other than those of the inventors. Furthermore, those reports that have attempted to correlate quantitative measurements with clinical assessments have found either no or poor correlations (Binder et al., 1996; Lohmann et al., 1991).

The best discussion of haze has been presented by Lohmann et al. (1991) who review corneal transparency and the various contributions of light attenuation, absorption, reflection, and scatter. In clinical observations using the standard slit lamp, light from the cornea consists of either reflected and/or scattered components that can be discriminated by their ability to change the polarization of light (i.e., reflected light is nonpolarizing whereas scattered light is). Using this difference, Lohmann et al. (1991) and Corbett et al. (1996a) have attempted to measure both the total amount of light and the scattering component using digital slit-lamp photomicroscopy with and without polarizers. In their studies they have shown that the light scattering from PRK patients initially peaks at 1 month postsurgery then declines and exhibits a second peak at 3 months after surgery, declining toward baseline thereafter.

Based on past studies, there are three potential sources for light scattering that are reviewed by Lohmann et al. (1991), including migratory or atypical keratocytes (Hanna et al., 1990; Tuft et al., 1989), microvacuoles or intralamellar inclusions (Marshall et al., 1988; Tuft et al., 1989), and newly synthesized atypical collagen (Hanna et al., 1990; Marshall et al., 1988; SundarRaj et al., 1990; Tuft et al., 1989). Based on *in vivo* investigations using confocal microscopy, Corbett et al. (1996a) suggest

that the early changes during the first month after surgery are related to keratocyte disturbances whereas later changes may reflect disturbances in the subepithelial region associated with deposition of material of keratocyte or epithelial origin.

These observations are also in agreement with more recent observations using *in vivo* confocal microscopic, three-dimensional reconstruction of the cornea of patients and rabbits receiving PRK (Moller-Pedersen et al., 1997, in press). In these studies, the total amount of backscattering light was correlated with the subcorneal region involved in light scattering. These studies have shown that there is a significant correlation between clinically described haze and the amount of backscattered light reflected from the photoablated stromal surface. Furthermore, analysis of the microscopic images suggests that the most prominent structures associated with light scattering come from activated or atypical keratocytes that may persist in the cornea for extended times and, in part, explain the late subepithelial haze seen by Corbett et al. in their studies. Haze intensity has also been correlated with the numbers of subepithelial keratocyte by Ramirez-Florez and Maurice (1996) based on a detailed histopathologic analysis of rabbit corneas following PRK. Furthermore, treatment of rabbit corneas with steroids showed a decrease in haze that was associated with decreased numbers of keratocytes. Although there are methodological problems in this study, the results are supportive of a role for the keratocyte in the production of haze.

The effect of steroids on haze is somewhat controversial with some studies showing an effect (Bergman and Spigelman, 1994; Ramirez-Florez and Maurice, 1996; You et al., 1995) and some studies not showing an effect (Gartry et al., 1992a; O'Brart et al., 1994). Steroids have been shown to decrease the number of keratocytes at the wound (Ramirez-Florez and Maurice, 1996) that is probably related to the ability of steroids to inhibit keratocyte proliferation (Lu et al., 1996) and migration (You et al., 1995). The discontinuation of steroids in patients receiving PRK has also been associated with the development of late onset corneal haze by two independent groups (Lipshitz et al., 1997; Meyer et al., 1996). Other agents that inhibit keratocyte or fibroblast proliferation, including interferon- 2b in rabbits (Morlet et al., 1993) and humans (Gillies et al., 1996), and 5 fluorouracil (Bergman and Spigelman, 1994) in rabbits, show decreases in the development of haze in treated eyes. Overall, it seems likely that steroids inhibit the development of haze and that inhibition is due to the inhibitory effects of steroids on keratocyte proliferation and migration.

On the other hand, increased haze and regression has been recently associated with exposure to solar radiation, particular UV light, that is a potential hazard for military personnel (Corbett et al., 1996b). Recent experimental studies by Nagy et al. (1997) have shown that pigmented rabbits receiving PRK are more susceptible to UV-B irradiation damage including anterior stromal extracellular vacuolization, increase keratocyte proliferation, and collagen disorganization. These cellular and extracellular changes also appeared to correlate with the development of increased haze potentially leading to increased fibrosis and regression. The clinical significance of these findings need to be further evaluated and the relative risk to military personnel determined.

In summary, the latest studies suggest that corneal haze following excimer PRK is most likely related to the activation and formation of atypical keratocytes at the subepithelial region of the PRK wound. Newly deposited atypical matrix or collagen may also contribute to longer lasting haze seen after 3 months; however, persistence of atypical keratocytes may also, in part, explain low levels of persistent haze. The effects of steroids, although somewhat controversial, appear to reduce haze by inhibiting keratocyte proliferation and migration to the subepithelial region. Other agents, interferon- 2b and 5 fluorouracil, which inhibit keratocyte proliferation and migration, appear to also reduce haze development. However, very little is known concerning the molecular mechanisms involved in keratocyte activation after PRK surgery and why the presence of atypical keratocytes produce backscattering of light. Furthermore, there is no explanation as to why some patients develop more haze, or more keratocyte

activation, than others. At this time there is no way to identify those patients that will develop more severe haze from those that will not.

The panel recommends that any clinical study that is supported by the DoD use an objective measure of haze that preferably identifies the location of light-scattering structures within the cornea such as used by Moller-Pedersen (1997). It would be of great value to test various haze measurement techniques and correlate values obtained to both clinical haze assessment and other visual function scores such as low-contrast visual acuity and glare to establish the best methods for assessing haze. In addition risk of UV exposure to haze development needs to be defined.

Regression

The refractive results after PRK show exceedingly wide variation with 70–100 percent of low myopes, 40–85 percent of moderate myopes, and 20–52 percent of high myopes achieving ±1.0 diopters of intended refraction 12 months post-PRK (Dutt et al., 1994; Gartry et al., 1992b; Maguen et al., 1994; Schallhorn et al., 1996; Seiler et al., 1994; Sher et al., 1994). Loss of initial refractive correction has also been noted with a myopic regression of typically 0.80–3.0 diopters occurring between 1 and 12 months post-PRK (Dutt et al., 1994; Gartry et al., 1992b; Maguen et al., 1994; Seiler et al., 1994; Sher et al., 1994). Factors which contribute to regression of refractive effect following PRK include (1) deeper ablations, (2) smaller photoablation diameters, (3) use of oral contraceptives, (4) solar radiation, and (5) ocular surface disorders (Corbett et al., 1996b).

As suggested by Durrie et al. (1995) patients can be broadly divided into three classes based on their response to PRK: type I patients who have a normal result and are within +1 diopter of emmetropia, type II patients that are overcorrected, and type III patients that are undercorrected. If all patients have received the appropriate amount of stromal photoablation, then the difference between the three types of patients can be best explained based on the individual wound healing responses such that type I patients heal normally, type II patients heal poorly, and type III patients heal aggressively (Durrie et al., 1995). This analysis is consistent with corneal pachymetry measurements of patients taken by Sabetti et al. (1994) that showed that type I patients generally had a normal amount of corneal thinning after surgery, whereas type II overcorrected patients showed an excessive thinning of the corneal stroma, and type III regressive patients showed a marked increases in thickness of the cornea up to 18 months after surgery.

Previous studies of human, primate, and rabbit corneas have related post-PRK regression of refractive effect (loss of initially achieved correction) to three potential causes: stromal thickening, (Del Pero et al., 1990; Fantes et al., 1990; Shieh et al., 1992; Tuft et al., 1989) epithelial hyperplasia, (Del Pero et al., 1990; Gauthier et al., 1995; Tuft et al., 1989) or distortion of existing tissue (Del Pero et al., 1990; Ramirez-Florez and Maurice, 1996). Epithelial hyperplasia has been reported histologically (Fantes et al., 1990; Hanna et al., 1989, 1990; Tuft et al., 1989) and clinically (Fagerholm et al., 1994). More recent studies by Gauthier and colleagues (1996a) who measured epithelial thickness after PRK using a modified Haag-Streit optical pachymeter have shown a 21 percent thickening of the epithelium in patients beyond 12 months after surgery. Regression analysis in this study showed approximately 18 μm of epithelial hyperplasia for every 1.0 diopter of regression with a significant correlation between epithelial thickening and regression. However, there appears to be an underlying 1.50 diopter of regression not explained by epithelial hyperplasia that is presumably related to a stromal component. Furthermore, in a companion paper evaluating the effect of mechanical epithelial removal in stimulating epithelial hyperplasia to reverse hyperopia

post-PRK, their was no clear relationship between any change in refraction and the change in epithelial thickness (Gauthier et al., 1996b).

Ramirez-Florez and Maurice (1996, 1997) have postulated that post-PRK regression of refractive effect in rabbit corneas is due to distortion of existing stromal tissue rather than growth of new tissue. Using a technique previously used by other groups (Tuft et al., 1989), these authors vitally stained the photoablated stromal surface with DTAF (dichlorotriazinyl aminofluorescein; a fluorescent dye that irreversibly labels exposed extracellular matrix proteins) and identified a thin layer of unlabeled newly deposited tissue above the photoablation zone using *ex vivo* fluorescent microscopy. However, Ramirez-Florez and Maurice did not measure corneal or stromal thickness *in vivo* and only used the *ex vivo* thickness of the thin layer of unlabeled new tissue as a measure of total post-PRK stromal thickening. It is, however, clearly questionable to extrapolate *in vivo* thicknesses from *ex vivo* measurements because of inherent difficulties with orientation of tissue sections, shrinkage, and deformation artifacts during tissue processing, etc., as also noted by other authors (Abad et al., 1996).

Recently, Moller-Pedersen et al., in press have measured the change *in vivo* corneal thickness of the stroma and epithelium following PRK in rabbits using quantitative *in vivo* confocal microscopy. In these rabbit eye studies they have shown that the stroma completely regenerates by 6 months after receiving 118 µm of stromal photoablation. No hyperplasia of the epithelium was noted in this study suggesting that, at least for the rabbit, regression can be completely accounted for by stromal repair. This observation is also consistent with the clinical observations on the use of steroids that leads initially to overcorrection followed by regression after cessation of therapy (O'Brart et al., 1994). Current studies in humans using *in vivo* confocal microscopy also support a major role for stromal repair in explaining regression of PRK.

In summary, the preponderance of data support a primary role of stromal fibrosis in explaining post-PRK regression. Hyperplasia of the corneal epithelium, although not apparent in animal studies, may contribute to changes in refraction early after injury when the epithelium is regenerating but its contribution to long-term regression has yet to be established. Clearly, more-detailed and quantitative studies are needed to answer this question.

The panel recommends that clinical studies by the DoD incorporate new instrumentation that can measure epithelial and stromal thickness and cellular responses to establish the cause of regression following PRK. Given that changes in the corneal thickness are the primary effect of PRK, it is interesting to note that the measurement of corneal thickness post-PRK is almost completely lacking in reported clinical investigations.

TEAR FILM, CYTOKINES, GROWTH FACTORS, AND HORMONES

Tears and PRK

Several investigators have suggested that PRK outcomes for dry eye patients is not as good as patients with normal tear flow rates (Stonecipher, 1996; Tervo et al., 1993). This was not confirmed when patients were divided into two groups based on their Schirmer tests: 6 mm/5 min and 10 mm/5 min (Tuunanen and Tervo, 1996.) No differences were observed in mean spherical equivalents, predictability of attempted corrections, uncorrected visual acuity, overcorrection, or regression between the two groups over a 1 year period. The effect of tear flow rates on haze, however, was not studied.

Following PRK in the human, changes occur in the flow rate and the composition of tears. Tear flow increases about ten fold by the first day following PRK and then decreases to normal by 7 days (Malecaze et al., 1997; Tervo et al., 1994b, 1997; Vesaluoma et al., 1995; Virtanen et al., 1995). Hypersecretion of tears occurs until the ablated area is covered with epithelial cells. Although total protein concentration in the tears does not change during this period, some components in the tears increase in concentration following PRK (Vesaluoma et al., 1997a). These include PDGF-BB, IL-6, and calcitonin (Malecaze et al., 1997; Tervo et al., 1995; Vesaluoma et al., 1997b). The concentrations of other tear components are unchanged or decrease over the first 2 days following PRK. Because of the tenfold increase in tear flow rates, the flux of the components across the cornea increases significantly. These tear components include the growth factors and cytokines; HGF, TNF , TGF- 1, and VEGF; the extracellular matrix proteins, extra domain A-containing fibronectin and tenacin; and the proteinase plasmin (Tervo et al., 1994b, 1997; Vesaluoma et al., 1995, 1997a,c; Virtanen et al., 1995). Other known growth factors in tears probably also increase in flux following PRK.   These include EGF and TGF- 2 (Vesaluoma et al., 1997a).

The sources of the tear components that increase following PRK have not been determined. Many are synthesized by the lacrimal gland whereas others are known to be synthesized by the cornea and/or the conjunctiva (Tervo et al., 1997; Vesaluoma et al., 1997a,b,c; Virtanen et al., 1995).   Wounding disrupts the tight junctions of the epithelial cells, suggesting that proteins synthesized by the stroma and basal epithelial cells may contribute to the proteins present in the tears following PRK. PDGF-BB may be released from macrophages invading the cornea (Ramirez-Florez and Maurice, 1996; Vesaluoma et al., 1997b).

Cytokines and Growth Factors and the Cornea

The increased HGF, TNF , TGF- 1 and VEGF, PDGF-BB, IL-6, and calcitonin flux across the cornea from tears probably plays a role in the regulation of the initial healing of the epithelium and stroma. PDGF activates phosphatidylinositol metabolism in epithelial cells, increases stromal synthesis of collagens types III and IV, and may increase collagenase levels (Vesaluoma et al., 1997b).   TNF   and IL-6 are proinflammatory cytokines. TNF has been suggested to contribute to haze and scar formation following PRK (Vesaluoma et al., 1997c).   This cytokine can stimulate fibronectin-induced epithelial migration and fibroblast proliferation. It also increases cell-matrix interactions by increasing the expression of integrins and the adherence of fibroblasts to collagen. TNF is chemotactic for neutrophils and macrophages. IL-6 stimulates the synthesis of collagens types I and III (Malecaze et al., 1997). HGF is a classical paracrine mediator of stromal–epithelial interactions (Tervo et al., 1997). It is synthesized by corneal stromal and lacrimal gland cells and then binds to epithelial cells. This growth factor modulates corneal epithelial cell proliferation, motility, and differentiation but has no effect on stromal keratocytes. TGF- stimulates fibronectin and collagen synthesis (Vesaluoma et al., 1997a). Calcitonin is a neuropeptide present in corneal nerves and is a strong vasodilator (Tervo et al., 1995).

Coordinated interactions between epithelial cells and keratocytes also involve the release of cytokines from the epithelium to stimulate keratocyte migration and division. Weng (Weng et al., 1997), in a study not related to PRK, found that IL-1 and IL-1 are key modulators in epithelial–stromal regulatory loop of the cornea. Corneal epithelial wounding releases IL-1 and IL-1 from epithelial cells, and these cytokines in turn up-regulate HGF and KGF mRNA and protein levels in keratocytes. HGF and KGF released by keratocytes modulate healing of corneal epithelial cells by regulating their proliferation, motility, and differentiation.

Growth Factor Treatment of PRK Corneas

Several growth factors have been tested for their ability to alter the healing process following PRK. These include bFGF, TGF- , and IF- 2 . In a human study, IF-2 delays epithelial healing by 2 days (Gillies et al., 1996). For corrections greater than 5.0 diopters, significantly less haze is observed between 3 and 12 months after PRK with IL- 2 treatment than without. No difference is observed between groups for corrections less than 5.0 diopters. IL- 2 treatment of rabbit corneas ablated for a -6.0-diopter correction show no effect on epithelial healing but did significantly reduce haze (Morlet et al., 1993).

Little is known about the effect of IF- on the cornea. This cytokine inhibits the growth of herpes simplex virus type 1 in human fibroblasts (Balish et al., 1992), protects mice from herpes simplex virus type 1 corneal disease (Hendricks et al., 1991), and stimulates the synthesis of complement C3 and C5 by human corneal fibroblasts (Rothman et al., 1991). In other tissues, IF- can inhibit the fibrotic response, fibroblast chemotaxis, proliferation, and collagen and proteoglycan synthesis (Morlet et al., 1993). It can also increase collagenase production.

Rabbit studies using bFGF for treatment of PRK eyes show a significant increase in epithelial healing rates and a significantly decreased amount of haze over the 13-week experimental period (David et al., 1995). There are numerous ways that bFGF affects the cornea. This growth factor is found in the extracellular matrix of the cornea and is synthesized by the cornea (Li and Tseng, 1995). bFGF increases keratocyte migration (Andresen et al., 1997), decreases the occurrence and severity of herpetic stromal keratitis in rabbits (Gamus et al., 1996), and stimulates epithelial healing of epithelial scraped wounds (Rieck et al., 1992).

In contrast to IF- 2 and bFGF, TGF- 1 has no significant effect on stromal haze associated with experimental PRK in rabbits (Myers et al., 1997). The trend is toward increased haze with TGF- 1 treatment but is not significant in part because of low numbers of experimental animals. One rabbit of nine treated with TGF- developed a corneal ulcer and was dropped from the study. These studies suggest that bFGF or IF-2 , but not TGF- 1, may be useful as a treatment following PRK.

Hormones and PRK

The hormone status of women influences the outcome of PRK. Although no differences in PRK outcome are observed in women on oral contraceptives relative to other premenopausal women, other conditions with greater hormone fluctuations can alter PRK outcome (McCarty et al., 1996; Sharif, 1997). Pregnancy is associated with myopic regression and increased haze following PRK. In one study, two women that were pregnant at the time of the surgery had poor outcomes with regression over the 12 months following surgery and increasing haze (McCarty et al., 1996). In another study, 12 of 18 eyes of nine women who became pregnant during the 12-month follow-up period after PRK had significant myopic regression and haze (Sharif, 1997). The other six eyes were stable. In addition, a correlation was observed between the difficulties of the pregnancy and the amount of myopic regression and haze. Postmenopausal women with or without hormone replacement had significantly poorer uncorrected vision than control premenopausal women as measured by LogMAR letters and Snellen lines (McCarty et al., 1996). In a third study, six of eight women showed stable refraction during pregnancy and labor. The other two had either myopic regression or a natural history of primary hyperopic shift (Hefetz et al, 1996). Fluctuating hormone levels associated with pregnancy, hormone replacement therapy, and menopausal status are

probably the reasons for the poor PRK results because corneal hydration is dependent on hormone levels.

PRK, Inflammation, and Corneal Degradation

Although PRK has been used successfully to treat epithelial erosions (Kremer and Blumenthal, 1997), epithelial erosions have been reported as a complication of PRK. Excimer laser PRK was performed on a 55-year-old woman using mechanical removal of the epithelium and a 6-mm ablation zone (Puk et al., 1996). One year later she had severe pain once a month due to recurrent erosions. The frequency increased to one every 7–8 days. Symptoms were relieved by anterior stromal puncture.

The influx of inflammatory cells post-PRK may depend upon post-PRK treatment. In a rabbit study, corneas were ablated with a VISX system using an optical zone of 3.5 mm, and then the animals were injected subconjunctivally with dexamethasone acetate (Ramirez-Florez and Maurice, 1996). Dexamethasone and Tobramycin were applied topically twice a day on the day before PRK and for 11 days post-PRK. Inflammatory cells were observed in the cornea beginning at 2 hours following PRK. The number of neutrophils peaked at day 1 and then disappeared by day 3. Macrophagelike cells increased from 6 to 72 hours and were absent by day 7. These cells were never observed more than 1 mm beyond the ablated zone-suggesting an ingress route through the tear film rather than from the limbal region. Use of a contact lens post PRK prevented the influx of these cells. The inflammatory cells may cause the oxidative damage noted in rabbits following excimer laser treatment (Hayashi et al., 1997). Oxidized lipids in the form of conjugated dienes increased 88 percent and ketodienes increased 198 percent following PRK. Most of the damage was at the surface of the ablated corneas. Fluorometholone, a phospholipase A_2 inhibitor reduces neutrophil influx into rabbit corneas at 10 hours following PRK (Phillips et al., 1993). Diclofenac, a phenylacetic acid-derived nonsteroidal anti-inflammatory drug, not only inhibits cyclooxygenase but also limits the pool of arachidonic acid thus inhibiting the production of lipoxygenase products. This drug reduces pain but does not reduce neutrophil influx at 10 hours following PRK.

Few studies have examined human corneas within the first 72 hours following PRK. In a human study, scarred corneas were ablated prior to penetrating keratectomy (Balestrazzi, et al., 1995). The corneas were treated with homatropine bromate and gentamicin ointment but not with corticosteroids or bandage contact lens. One cornea was removed at 3 days post-PRK and examined by light and transmission electron microscopy. No inflammatory cells were observed in this cornea removed at 3 days or other corneas taken at 3, 5, and 13 months.

Little is known about proteinases and their role in the healing process of the cornea following PRK. Plasmin flux across the human cornea following PRK is elevated because of increased tear flow but not because of higher plasmin concentration in tears (Tervo et al., 1994b). This serine proteinase cleaves numerous proteins but its main target is fibrin (Ramsby and Kreutzer, 1993). In addition, plasmin can activate matrix metalloproteinases. The role of tear plasmin is not clear. Treatment of PRK corneas for 3 weeks with aprotinin, an inhibitor of plasmin and other serine proteinases, had no observable effect on the wound-healing process (O'Brart et al., 1994). Matrix metalloproteinase levels have only been reported in one study (Azar et al., 1996). The 72 kDa gelatinase (MMP-2, gelatinase A) was observed in the epithelial layer of the PRK-treated stromas at 6–12 hours and the 92 kDa gelatinase (MMP-9, gelatinase B) was observed at 18 hours. In the stroma, the 72 kDa gelatinase was constitutively expressed and was observed through the 90-hour observation period following PRK. The 92 kDa gelatinase was expressed in the stroma at 6–18 hours post-PRK. These results are consistent with the pattern of metalloproteinase expression following

wounding of the epithelial plus the stromal layers (Fini et al., 1992; Matsubara et al., 1991).

Keratitis is an uncommon complication of PRK; however, bacterial, fungal, and sterile keratitis have been reported (Amayem et al., 1996; Edmison, 1997; Sampath et al., 1994; Wee et al., 1997). *Staphylococcus epidermis, Streptococcus pneumoniae, Pseudomonas aeruginosa, Staphylococcus aureus* were isolated from post-PRK ulcers (Amayem et al., 1996; Sampath et al., 1994; Wee et al., 1997). Patients with these infections received a bandage contact lens and either no antibiotic treatment or only one treatment of antibiotics following PRK. One case of reactivation of herpes simplex was reported (Edmison, 1997). Sterile immune keratitis, that generally results in scarring and loss of best-corrected acuity, has a reported incidence of 1 in 300 following PRK (Teal et al., 1995). Patients with keratitis were treated with nonsteroidal anti-inflammatory drugs (diclofenac or ketorolac), antibiotics (Tobrex, Ciloxan, or Polytrim), and soft contact lenses. Diclofenac reduces pain and PGE_2 production but does not prevent the influx of leukocytes into the cornea (Phillips et al., 1993). The incidence of keratitis may be increased with use of bandage contact lens, but the improvement in patient comfort outweighs the risk (Edmison, 1997).

Conclusions

The effects of hormones and growth factors need to be studied further. The initial studies of the PRK outcomes on pregnant and postmenopausal women suggest that women in these groups are poor risks for PRK. This is of particular concern for the military who will have young female recruits of child-bearing age that may adversely benefit from this surgery. Long-term studies are needed in this area and in the area of growth factor effects on the corneal haze, regression, and wound healing following PRK.

Very little is known about the influx of inflammatory cells in humans following PRK. Confocal microscopy may be the best way to study this process because it is a noninvasive technique. The earliest time point that human corneas have been studied using this technique is 7 days (Linna and Tervo, 1997). The pattern of inflammatory cell invasion from the tear film or the limbus may predict corneas that would go on to ulcerate. It is recommended that clinical studies evaluate the early inflammatory response and correlate polymorphonuclear leakocyte (PMN) infiltration to development of haze and regression as objectively measured using *in vivo* confocal microscopy.

CORNEAL EPITHELIUM

Healing of Epithelial Debridement

Upon epithelial debridement, as occurs following PRK, the epithelial cells migrate to cover the denuded corneal surface and do not engage in proliferation until 3 days after injury (Katakami et al., 1988). This initial inhibition of epithelial cell proliferation following laceration may result from inflammatory response (e.g., the invasion of PMN to the injured corneas). The cessation of epithelial cell proliferation is concomitant with the appearance of PMN in lacerated corneas. It is possible that PMN may modulate epithelial cell proliferation. However, there are few studies on the inflammatory responses immediately following PRK procedures. It should be noted that the administration of steroids causes the delayed invasion of inflammatory cells (e.g., PMN, macrophages). It remains to be proved whether it may be beneficial to administer

steroids and/or other anti-inflammatory agents after PRK (Binder et al., 1994; Tengroth et al., 1993; Tervo et al., 1992).

At early stages of wound healing of epithelial debridement, the migration of epithelial cells, like other cell types, is mediated by integrins, the cell surface receptors of extracellular matrix (Latvala et al., 1995; Murakami et al., 1992; Paallysaho and Williams, 1991; Tervo et al., 1992). However, the integrin that mediates epithelial cells migration has not been well characterized. The 6 4 integrin is a component of hemidesmosomes (Stepp et al., 1990). Immunostaining with anti- 6 integrin antibody showed a discontinuous distribution of 6 integrin subunit underlying the basal epithelial cells up to 12 months after PRK, whereas in normal cornea the distribution of the subunit is continuous (Beuerman et al., 1994; Fantes et al., 1990; Latvala et al., 1995; Sher et al., 1991; Stepp et al., 1993, 1996). Similar distribution of laminin in PRK-treated and untreated corneas were found (Latvala, et al., 1995). The number of hemidesmosomes was also reduced (Beuerman, et al., 1994; Chang, et al., 1996b). These observations may be associated with recurrent epithelial defects following PRK.

Epithelial hyperplasia is often observed after PRK, specifically the central cornea is often thickened with ten or more epithelial cell layers (Balestrazzi, et al., 1995; Beuerman, et al., 1994; Fantes, et al., 1990; Sher, et al., 1992). The phenotypic expression of the cornea-specific keratin K12/K3 pair after PRK has not been determined. Expression of K12/K3 keratin pair characterized the corneal type epithelial differentiation (Chaloin-Dufau et al., 1990; Chen et al., 1994; Kao et al., 1996a; Liu et al., 1993b; Moyer et al., 1996; Wu et al., 1994; Zhu et al., 1992). For example, examination of regenerated epithelium by immunostaining and western blot analysis revealed a normal pattern of keratin 12 expression in partial epithelial defects, but not in total epithelial defects (Chen et al., 1994; Moyer et al., 1996). These observations are similar to previous reports indicating that regenerated corneal epithelium expresses keratin 12 following mild alkali burns in which the limbal stem cells were preserved (Zhu et al., 1992). It has been suggested, however, that the corneal epithelial cell-specific expression of K12/K3 keratin pair can be modulated by tissue environments (e.g., the composition of basement membrane components) (Kurpakus et al., 1992).

Because PRK removes the corneal epithelial basement membrane and the anterior portion of stroma, the epithelial cells that migrate onto the denuded corneal surface must bind to a stromal extracellular matrix composed of fibrillar collagen instead of basement membrane. The consequence of such a tissue environmental change on corneal epithelial cell functions is not known. It has been suggested that the corneal and conjunctival basement membranes profoundly affect the differentiation functions of corneal and conjunctival epithelial cells (Kurpakus et al., 1992). Thus, it is very likely that corneal epithelial cells adhering to the stromal matrix may change their functions and subsequently produce adverse effects on the activated keratocytes, which are responsible for the repair of stromal wounds. It remains largely unknown how the binding of corneal epithelial cells to stroma alter the epithelial cell phenotypes following PRK.

Epithelial Cell Attachment

A number of studies examined the epithelial basement membrane after PRK. To determine the integrity of attachment of the epithelium to the ablated stroma, Latavala et al. (1995) investigated basement membrane laminin and hemidesmosomes. Immune reaction assay for laminin and hemidesmosomal integrins 6 and 4 in normal cornea showed them as continuous bands at the basal aspect of basal epithelial cells. After ablation the re-epithelialized area showed that secondary epithelial defects 1 mm or larger in diameter persisted in 77 percent of the eyes. At 6 months post-PRK, the

immune reaction assay showed multiple focal discontinuities in the basal aspect of basal epithelial cells. After 12 months, subepithelial immunoreaction for α6 and β4 and laminin resembled that in the normal (nonablated) area (i.e., continuous bands). Some bands, however, still contained a few interruptions. This study demonstrated slow structural healing of PRK wounds; at 12 months post-PRK the cornea still showed changes typical of wound repair, presenting the possibility of risk from epithelial erosion for as long as a year after ablation.

Beuerman et al. (1994) found that in ablated monkey epithelium there was a statistically significant decrease in the density of hemidesmosomes in the treated areas for up to 12 months. Chang et al. (1996b) found that in the rabbit the extent of hemidesmosome formation was abnormal for up to 12 weeks.

In another investigation, Latavala et al. (1996b) used cat corneas that were ablated to 5.0 diopters to determine by indirect immunohistochemistry the effects of PRK on SPARC (secreted protein, acidic and rich in cysteine), an extracellular glycoprotein that is especially active in tissues undergoing remodeling and that promotes the rounding of cells and inhibits cell spreading. All wounds were covered by a multilayer epithelium after 4–5 days. There was a transient (1–6 days after wounding) intense immunoreaction for SPARC at the basal aspect of the basal epithelial cells. The SPARC reaction began from the wound edge and was not observed adjacent to the flattened and actively migrating single-layered epithelial cells of the leading edge. It was found to be related only to the recently migrated basal cells in the multilayered epithelium that assumed a round shape. This result suggests that the transient appearance of SPARC protein under the healing epithelium reflects the protein's role in the regulation of epithelial cell migration and shape during the healing process, probably playing a part in modulating cell–extracellular matrix interactions.

Azar et al. (1996) demonstrated in rat corneas the expression of matrix metalloproteinases (MMP-2 and MMP-9) in the epithelium for 6–24 hours after ablation and hypothesized that they play an important role in wound healing after PRK.

Reassembly of Basement Membrane

PRK ablates the corneal epithelial basement membrane; therefore, the regenerated corneal epithelial cells need to synthesize components (i.e., collagen types IV and VII and laminin for a new basement membrane underlying the epithelium [Stock et al., 1992; Tervo et al., 1992)]). It has been noted that the compositions of basement membranes at different organ systems differ from each other; thus the specific basement membrane serves the special needs of given tissues (Hay and Zuk, 1995). The corneal epithelial basement membrane, like other basement membrane, contains collagen α1(IV), α2(IV), α3(IV), α4(IV), and α5(IV) chains and laminin (Ishizaki et al., 1993b; Ishizaki et al., 1997; Kolega et al., 1989; Ljubimov et al., 1995). However, the immunostaining with anti-α1(IV) and anti-α2(IV) antibodies failed to label the corneal epithelial basement membrane. It was suggested that the presence of other collagen (IV) chains and/or other extracellular components might mask the epitopes recognized by the antibodies (Ishizaki et al., 1993b; Ljubimov et al., 1995). It is of interest to note that the anti-α1(IV) and anti-α2(IV) antibodies label the basement membrane of injured corneal epithelium that have healed for more than 7 days (Ishizaki et al., 1997). The accessibility of these epitopes indicates that the structure of the newly synthesized basement membrane differs from the structure of normal basement membrane. Presumably, similar changes of basement membrane would take place following PRK. However, no direct evidence for such changes is available.

In addition to the possible compositional changes, the wound healing of PRK also fails to generate continuous basement membranes underlying the corneal epithelium as noted above. Immunostaining and transmission electron microscopy have

demonstrated the discontinuity of the newly synthesized basement membrane (Beuerman et al., 1994; Fantes et al., 1990; Sher et al., 1992; Tervo et al., 1992). It is not known whether the discontinuity of the basement membrane contributes to recurrent epithelial defects and/or other cornea abnormalities (e.g., hyperplasia, haze observed in PRK-treated corneas). Such incomplete regeneration of the basement membrane is opportunistic for epithelial cells to exert effects on keratocytes function, or vice versa (Hay and Zuk, 1995). Subsequently, such a direct dialog between epithelial cells and keratocytes may lead to undesirable formation of opaque scar tissues in cornea. However, further studies are necessary to verify this speculation.

Epithelial Barrier Function

The corneal epithelium maintains a barrier from the external milieu. To be effective after PRK, the basal epithelial cells must attach themselves to the underlying tissue, and the surface epithelial cells must provide a barrier with their cell membranes and intercellular tight junctions. After PRK, the ablated stroma is recovered with a new epithelium within a few days. However, in spite of this rapid re-epithelialization, functionally the epithelium heals much more slowly, with some of its components taking up to a year to regain their normal function.

The return of the epithelial barrier function to its normal state was investigated by Kim et al. (1996) in rabbit corneas after shallow (3.3 diopters) and deep (5.0 diopters) ablations. Uptake of 5,6 carboxyfluorescein to measure corneal epithelial permeability showed an initially elevated permeability that returned to normal after 2 weeks in the shallow-ablated corneas and after 4 weeks in the deep-ablated corneas. A ruthenium red assay to measure epithelial tight junction integrity revealed that after 4 weeks the dye did not penetrate the epithelium of shallow-ablated corneas, but that in the deep-ablated corneas the superficial cell layer was stained by ruthenium red, indicating imperfectly formed tight junctions. This study demonstrated that, after a month, epithelial barrier function returned to normal in shallow-ablated corneas, but not in deep-ablated corneas.

Chang et al. (1996b) investigated the permeability of Na-fluorescein in post-PRK rabbit corneas and found that the epithelial barrier was subnormal for 4 weeks before returning to normal. Morphological examination of these corneas revealed that tight junctions between some surface cells were seen only after as much as 9–12 months post-PRK.

Corneal Innervation

The normal mammalian cornea is richly innervated and is extremely sensitive to touch, pain, heat, and cold. Different fiber populations, such as cholinergic and adrenergic (Laties and Jacobowitz, 1964) and peptidergic (Shimizu et al., 1982; Tervo et al., 1982), contribute to its innervation.

The pattern of epithelial and stromal innervation has been extensively described in an animal model *in vitro* using gold chloride staining techniques (Pallikaris et al., 1990; Ishikawa et al., 1994a,b), monoclonal antibodies (Trabucchi et al., 1994), and a histochemical acetylcholinesterase reaction (Tervo et al., 1994a).

Human corneal innervation *in vitro* has also been extensively described (see, e.g., Ueda et al., 1989). Anteriorly directed nerves, leaving the subepithelial nerve plexus, perforate Bowman's layer at an estimated 400 fixed peripheral sites to enter the basal epithelial cell layer. Other nerves enter the corneal basal epithelium at the limbus. Together they form the basal epithelial nerve plexus. Nerves of the plexus run radially just anterior to the basal lamina, beneath and between basal epithelial cells. Each nerve

contains between 1 and 40 axons, and adjacent nerves intermingle by way of numerous connecting elements. The basal epithelial nerves have varicosities (beads) that have been described as axonal efferent and sensory terminals (Matsuda, 1968; Schimmelpfenning, 1982; Ueda et al., 1989). Corneal sensitivity is not the same throughout the cornea, but is correlated with nerve density; it is greatest at the center and lowest in the superior portion of the cornea (Ishikawa et al., 1994a,b).

Human corneal innervation has also been studied *in vivo* using confocal instruments. Cavanagh et al. (1990) used the scanning pinhole confocal microscope to investigate nerve branching and beading of the basal epithelial nerve plexus, and Auran et al. (1995) described corneal epithelial nerve dynamics.

Influence of Corneal Innervation on Epithelial Healing

Corneal innervation is an important factor in maintaining normal corneal structure and function. Denervation leads to epithelial dysfunction, indicating that corneal nerves have a trophic influence on the corneal epithelium (see the review by Latvala et al., 1996a). Denervation has been demonstrated to decrease epithelial mitosis rate (Sigelman and Friedenwald, 1954; Mishima, 1957), result in weak attachment of epithelial cells and persistent epithelial defects (Araki, 1996), and result in a significant impairment in healing of epithelial abrasions and a significant increase in relative epithelial permeability (Beuerman and Schimmelpfenning, 1980). All of these conditions have important clinical consequences.

Furthermore, the differences in re-epithelialization that are apparent between shallow and deep ablations may also be influenced by loss of corneal nerves. Because the extent of damage to the nerves located in the anterior stroma appears to be the only factor that changes with increasing ablation depth, this points to the possibility that neurotrophic factors may play a role in healing after PRK .

Reinnervation in Ablated Corneas

Complete reinnervation of the epithelium in the ablation zone takes place long after the 4–7 days (depending on species) that it takes for the epithelium to cover the ablated area.

In the animal model, Pallikaris et al. (1990) showed reinnervation of the epithelium after 4 weeks. Trabucchi et al. (1994) demonstrated that at 4 weeks the subepithelial nerve plexus was present, but somewhat disorganized.   Tervo et al. (1994a) found that the epithelium was completely reinnervated after 3 months, but that the stromal innervation was still abnormal.

Corneal sensitivity, which is related to reinnervation, was found by Ishikawa et al. (1994c) to be higher than normal (i.e., hypersensitivity) for 42 days post-PRK, after which it returned to normal.   Loya et al. (1994) determined that, after a transient decrease, sensitivity returned to normal after 8 days, then increased (hypersensitivity) for a few days, returned to normal by day 14, and remained normal thereafter.

Ishikawa et al. (1994a) studied nerve regrowth and sensitivity together in the same corneas. They found that after about 4 weeks post-PRK epithelial innervation was higher than normal and that corneal sensitivity was higher than normal for 7 months (i.e., a hypersensitivity), after which it returned to normal. They were the first to observe a correlation between increased sensitivity and increased nerve density in the same cornea after excimer laser ablation. However, it should be noted that they ablated only the epithelium, leaving the rest of the cornea intact.

In human patients Campos, et al. (1992a) found that corneal sensitivity was lower than normal for 6 weeks after PRK before returning to normal. Ishikawa et al.

(1994a) found that corneal sensitivity was lower than normal for 6 months before returning to normal. Linna and Tervo (1997) detected immature nerves in the epithelium after 7 days, but found that even after 34 months post-PRK the morphology of the subepithelial nerves was still abnormal.

Considering the long time that it takes for corneal innervation to return to its normal state, the relationship between reinnervation, epithelial healing, and long-lasting epithelial defects present in some patients after PRK warrants further study.

Scraping versus Photoablation of the Epithelium

There is very limited information available regarding whether it is preferable to photoablate or scrape away the epithelium prior to PRK. There is only a single report in which this issue was addressed extensively (Gimbel et al., 1995). However, the experimental design in this study was not completely appropriate, which means that a definitive study is still required to determine whether photoablation or scraping is a preferable procedure prior to PRK.

This single report (Gimbel et al., 1995), a retrospective matched controlled study, analyzed the refractive outcome of 46 eyes after excimer laser PRK. Half of the eyes had the corneal epithelium ablated with the excimer laser whereas the other half had mechanical removal. Topical corticosteroid dosing was different in the two groups. All PRK surgery was performed by the same individual. The two groups were analyzed for statistical differences in refractive outcomes and corneal haze after 6 months. The results show that at no point postoperatively was there any significant difference in the mean refractive outcome or variance of the refractive results between the two groups, although there was a *trend* toward greater correction with laser ablation of the epithelium. There was no statistical difference in the amount of stromal haze by slit-lamp microscopy in the two different debridement groups.

The results of this study are open to question because of some confounding effects: (1) there was a variable use of corticosteroids between the two groups; (2) the smallness of sample size; (3) the retrospective nature of the study; and (4) the lack of randomization. Therefore, it is not apparent whether the final refractive outcome is dependent on the epithelial removal technique.

A comment is warranted in support of photoablation as being preferable to scraping away of the epithelium. If it is accepted that minimizing keratocyte apoptosis in response to epithelial removal decreases the extent of keratocyte activation and stromal remodeling, there is some evidence supporting laser ablation as being preferable to scraping. With laser ablation, it was found that the frequency of keratocyte apoptosis was less than that after scraping away of the epithelium (Wilson, 1997a).

Conclusions

Any epithelial dysfunction presents the risk of inflammation, infection, and ulceration. The possibility of an impaired barrier function in spite of complete re-epithelialization must be taken into account when prescribing artificial tears or other eye medication. Epithelial attachment complexes (hemidesmosomes, basement membrane, and anchoring fibrils) show a segmented pattern of morphology months after PRK. Abnormal basement membrane, one that is not completely healed and does not adhere properly to the underlying stroma, presents a risk of epithelial erosions. Furthermore, it is unclear what method—scrape or transepithelial photoablation—produces the least damage to the underlying cornea and leads to the best visual outcome. It is recommended that clinical studies objectively correlate the method of epithelial removal

to depth of injury and production of haze and regression. Also, basic studies of epithelial differentiation and its susceptibility to infection need to be performed.

CORNEAL STROMA

Stromal Keratocyte Apoptosis

Apoptosis (programmed cell death) is a normal process that occurs in essentially all multicellular organisms during tissue renewal, development, and morphogenesis. It occurs when cells have sufficient time to organize and participate in their own demise (Cotter and Al Rubeai, 1995). It differs from necrosis in which cell contents are spilled into the surrounding tissue space provoking an inflammatory response. Unlike necrosis, it is a mechanism for the orderly elimination of unwanted cells. It is an involutional process and occurs with minimal collateral damage to surrounding cells and tissues. Its characteristics are cell shrinkage, membrane bleb formation, loss of cell-to-cell contact, aggregation of chromatin into dense masses attached to the nuclear membrane, formation of apoptotic bodies, nuclear fragmentation, and finally phagocytosis. Biochemically, apoptosis is recognized frequently by extensive cleavage of DNA into oligonucleosome-sized fragments (Cohen and Duke, 1992).

A relationship of apoptosis to PRK has been suggested that connects the untoward side effects of PRK, including transient epithelial hyperplasia, subepithelial corneal haze, and refractive regression, with the increased frequency of apoptosis in keratocytes subsequent to PRK (Wilson, 1997). There are a number of suggestive studies indicating that stromal keratocyte apoptosis is cytokine mediated (Mohan et al., 1997; Wilson et al., 1996a,b). It is hypothesized that the extent of resultant keratocyte activation may be dependent on the magnitude of keratocyte death resulting from PRK. It must be emphasized that there is no direct evidence that modulating keratocyte apoptosis will influence the final result of refractive surgery. Nevertheless, corneal wound healing has an effect on predictability and stability of the refractive correction achieved by PRK (Del Pero et al., 1990; Fantes et al., 1990; Wu et al., 1994). Accompanying apoptotic activation by cytokines, death gene expression occurs that is countered by antideath gene expression and it acts to offset increases in apoptotic frequency (Gao et al., 1997; Wilson et al., 1996b). This type of complex regulation of keratocyte apoptosis frequency makes it feasible to target (1) development of cytokine receptor antagonists that could inhibit receptor stimulation and decrease the frequency of apoptosis in keratocytes and (2) identification of strategies that could stimulate antideath gene expression. By inhibiting apoptosis through receptor blockade and stimulation of antideath gene expression, subsequent keratocyte activation may be decreased. These strategies may suppress the development of subepithelial haze, refractive regression, and epithelial hyperplasia. Should these strategies be successful, a more favorable PRK outcome may be possible.

It has been hypothesized that apoptotic control by corneal epithelial cells of keratocytes evolved as a protective mechanism against extending viral infection of corneal epithelial cells to underlying keratocytes in the stroma (Wilson et al., 1997). This hypothesis is supported by unpublished data of Wilson et al., (1997b) demonstrating superficial keratocyte apoptosis in association with primary herpes simplex virus infection in the rabbit. Should this finding be validated, the intriguing hypothesis arises that epithelial debridement in PRK is interpreted as a viral infection which results in the induction of widespread apoptosis in superficial keratocytes.

Apoptosis is a receptor-mediated response and is under autocrine and paracrine control (Wilson, 1997). Stimulation of receptors on the same cells from which the cytokine is released is designated as autocrine control whereas if a different cell type is

stimulated by the released cytokine it is referred to as paracrine control. Some of the cytokines that are released by corneal epithelial cells after injury or death that can affect apoptosis by keratocytes are IL-1 and IL-1 .   These two cytokines can stimulate apoptosis of the keratocytes *in vitro* and *in vivo.* It is unlikely, however, that IL-1 is the only cytokine mediating this response because keratocyte death cannot be interrupted by microinjection of IL-1 receptor antagonist beneath the corneal epithelium prior to debridement (Wilson et al., 1996a). Another redundant apoptosis mediating system is the Fas/Fas ligand complex (Mohan et al., 1997; Wilson et al., 1996b). It is expressed *in vivo* in corneal cells, and stimulation of the Fas triggers apoptosis of cultured keratocytes.   The relationships between IL-1 and Fas control of apoptosis are not known. In other words, it has not been established whether epithelial injury triggers keratocyte apoptosis through release of IL-1 followed by the induction of Fas ligand in keratocytes or if these cytokines elicit their paracrine effects independent of one another. Therefore, it is pertinent for improving the outcome of the PRK procedure to support projects proposing to further characterize the regulation of apoptotic phenomena in the corneal epithelium and stroma.

The evidence that the loss of the epithelium in PRK induces keratocyte apoptosis as a consequence of cytokine release is indirect. However, it has been shown that herpes simplex virus infection of corneal epithelial cells induces apoptosis of the underlying keratocytes (Wilson et al., 1997). The potential role of IL-1 release by epithelial cells in initiating apoptosis of stromal keratocytes in response to epithelial loss was investigated *in vitro* and *in vivo* (Wilson et al., 1996a). Apoptosis was identified based on an evaluation of keratocyte and stromal fibroblast cell morphology in control and epithelial debrided mouse corneas using transmission electron microscopy.   Nuclear DNA fragmentation was detected with the TUNEL (transferase with dUTP-biotin nick end labeling) assay for 3'-hydroxyl DNA ends. The effect of IL-1 on keratocytes *in vivo* was determined by the microinjection of IL-1 into the central corneal stroma through a limbal entry site. The *in vitro* effects of IL-1   and IL-1   were determined with primary cultures of corneal stromal and dermal fibroblasts.   Indeed debridement caused apoptosis and the disappearance of keratocytes from the underlying stroma based on the above-mentioned morphological and biochemical criteria.   This response may be mediated in part by IL-1   release from epithelial cells in response to injury because microinjection of IL-1   into the central stroma also caused apoptosis and reorganization of the keratocytes. The reason that the evidence for keratocyte disappearance is indirect is that (1) keratocyte death cannot be interrupted by microinjection of IL-1 receptor antagonist beneath the corneal epithelium prior to debridement; and (2) either a change in the physical environment of the anterior stroma or physical damage to the keratocytes by debridement could also initiate keratocyte apoptosis.

As it is clearly shown in several species that the incidence of apoptosis increases in keratocytes underlying a epithelial wound, it is important to understand whether the inhibition of their cell death could affect PRK outcome. This question warrants further attention because keratocyte apoptotic death initiates remodeling of the stroma through keratocyte activation. Such an effect sets in motion keratocyte proliferation, migration, and laying down of replacement stroma underneath the wound as discussed below. Remodeling as a consequence of keratocyte activation may help explain subepithelial haze, eventual regression of a refractive correction, and transient epithelial hyperplasia in recovering PRK patients. Subepithelial haze may arise from an increase in stromal keratocyte density. Refractive regression occurs as a result of increases in biosynthetic activity in activated keratocytes. These increases elaborate a new stromal matrix that replaces photoablated stroma, resulting in loss of the refractive correction obtained with the PRK procedure. On the other hand, transient epithelial hyperplasia is a consequence of a paracrine mechanism in which there are increases in the release of the mitogens, HGF, and KGF from keratocytes subsequent to epithelial debridement (Li et al., 1996; Wilson et al., 1993, 1994). Therefore, one route of investigation that could improve PRK

success is to probe further for the specific cytokines that are released by epithelial cells and keratocytes and that stimulate specific receptors to mediate keratocyte apoptosis.

There are other indications that apoptosis of stromal keratocytes occurs in response to epithelial debridement. Along with the above-mentioned apoptotic events, the gene and protein expression were detected of various other death and antideath genes. The mRNA transcripts were detected for other modulators of apoptosis in primary cultures of human corneal epithelial cells and stromal fibroblasts (Wilson et al., 1996b). They include Bax and an interleuken-converting enzyme that are referred to as death genes. On the other hand, in post-PRK rabbit corneas, increases were detected in the protein expression of the antideath gene bcl-2 (Gao, et al., 1997). These findings introduce the intriguing notion that keratocyte apoptosis in response to epithelial wounding could be inhibited by driving the overexpression of bcl-2 but inhibiting the expression of death genes.

Review of Stromal Repair

Corneal strength and transparency depend on the development and maintenance of an organized stromal extracellular matrix of uniformly small-diameter collagen fibrils with consistent interfibrillar spacing and normal epithelial and endothelial cells. The regularly packed stromal collagen fibrils are organized into lamellae with adjacent layers approximately perpendicular to one another (Hay, 1980; Linsenmayer et al., 1990). The mechanism that governs the formation of collagen lamellae is not well understood. It has been suggested, however, that the presence of proper ratios of different collagen types may play an important role in the formation of a well-organized collagenous matrix (Birk and Trelstad, 1984; Linsenmayer et al., 1990, 1993). Other extracellular matrix components (e.g., proteoglycans and glycoproteins) are essential for the development and maintenance of transparent corneas (Hahn and Birk, 1992; Hassell et al., 1983; Linsenmayer et al., 1990; Oldberg et al., 1989). It has been demonstrated that both heterotypic collagen fibrils and proteoglycans are major extracellular components in corneal stroma (Chen et al., 1994; Hassell et al., 1983; Hay, 1980; Linsenmayer et al., 1990; Liu et al., 1993a). In addition, appropriate hydration of corneal stroma, which is modulated by stromal proteoglycans content, and functions of corneal endothelial and epithelial cells is essential for the maintenance of corneal transparency (Asari et al., 1992; Stiemke et al., 1991).

Injuries to ocular tissues frequently lead to impaired vision because the healing process seldom restores the normal tissue functions. For example, corneal wound healing often fails to regenerate normal transparent tissues; instead, opaque scar tissues are formed (Ishizaki et al., 1993a; Matsuda and Smelser, 1973; Sakai et al., 1991). It is of interest to note that the process of wound healing is similar to that of tissue morphogenesis during embryonic development, because both processes are characterized by cell migration, tissue reabsorption, and synthesis of new tissue components (Caplan et al., 1983; Hay, 1980; Klymkowsky and Karnovsky, 1994; Raghow, 1994). For example, it has been noticed that the cellularity in granulation tissues changes dramatically during wound healing (Darby et al., 1990). Granulation tissue fibroblasts have traditionally been thought to derive locally from resident or nearby fibroblasts surrounding the wounds (Eddy et al., 1988; Oda et al., 1988; Skalli and Gabbiani, 1988). Thus the process of fibroblast migration resembles cell migration during embryonic development. The precise elements of wound healing, however, differ from that of morphogenesis during embryonic development. Thus, corneal wound healing often leads to the undesirable formation of opaque scar tissues (Raghow, 1994). During embryonic development a balanced distribution of various macromolecules in the tissue is achieved by way of a discrete, yet overlapping, series of biosynthetic and restructuring events that result in the combined molding of tissues and organs into the highly

restricted and specialized states required for adult function (Caplan et al., 1983; Hay, 1980; Klymkowsky and Karnovsky, 1994). It is possible that wound healing fails to regenerate normal tissues, because these fibroblasts that migrate into the wounds fail to synthesize various macromolecules (e.g., different collagen types and proteoglycans, in the proper proportions in order to restore tissue functions (Cintron et al., 1981, 1988; Raghow, 1994).

　　　PRK involves the epithelial debridement and ablation of epithelial basement membrane, Bowman's membrane, and a portion of stromal collagenous matrix as noted above (Balestrazzi et al., 1995; Binder 1994; Chang et al., 1996b; Fantes et al., 1990; Hanna et al., 1992; Moller-Pedersen et al., 1997; Rawe et al., 1992; Winter et al., 1997). Thus, the wound-healing processes following PRK involve re-epithelialization of denuded corneal surface, reassembly of basement membrane underlying corneal epithelium, and formation of granulation tissues in stroma. In addition, the healing also complicated by the potential interaction between epithelial cells and stromal keratocytes that are normally separated by the basement membrane underlying the epithelium (Fini et al., 1996). It is of interest to note that PRK inflicts minimal damage to corneal endothelium, if there is any (Kent et al., 1997; Sano et al., 1996).

　　　To become widely accepted, a refractive surgical procedure such as PRK must predictably and permanently correct refractive errors without risk of permanent visual loss. Although PRK produces statistically encouraging results of correcting myopia, the outcome of PRK is hard to predict at an individual basis (Gartry et al., 1992b; Hanna et al., 1992; Moller-Pedersen et al., 1997; Sher et al., 1991, 1992). It is occasionally compromised by regression and complicated by haze because of undesirable scar tissue formations. In general, there is a lack of knowledge of cell and molecular biology in respect to the mechanism that governs the regulation of wound healing including PRK. Therefore, the most significant challenge ahead is how to identify the individuals who are at high risk of receiving PRK for correcting myopia and modulation of wound healing to regenerate transparent corneas. To achieve these goals, more research is needed to examine the cell and molecular biology of corneal wound healing.

Cellular Mechanisms of Stromal Wound Healing

　　　Histological examinations have indicated that wound healing of PRK leads to formation of disorganized stromal collagenous matrix (Fantes, et al., 1990; Hanna, et al., 1992; Rawe, et al., 1992), similar to what have been described in other wound healing models (Ishizaki et al., 1994, 1997; Sakai et al., 1991).   However, there is little information available regarding the regulatory mechanisms of PRK wound healing at molecular and cellular levels.   The following subsections summarize our current understanding of stromal injury and corneal wound-healing response. It is believed that wound healing of PRK would involve similar molecular and cellular mechanisms.

Destruction of Collagen Lamellae in Injured Corneal Stroma

　　　Collagen constitutes about 80 percent of the organic constituents of the corneal stroma (Cintron et al., 1981; Kao et al., 1982), with orthogonal collagen lamellae contributing to corneal transparency (Hay, 1980; Linsenmayer et al., 1990). The collagen lamellae are frequently destroyed during wound healing in the cornea.   Corneal scar tissues are characterized by the presence of a disorganized collagenous matrix with irregular fibril spacings and larger fibril diameters (Cintron et al., 1982; Ishizaki et al., 1993a; Ishizaki et al., 1997; Matsuda and Smelser, 1973; Sakai et al., 1991).

　　　Electron microscopic examination revealed that in normal adult rabbit corneal stroma the collagen fibrils are arranged in characteristic lamellae sheets with uniform

fibril diameter and fibril spacings, and the lamellae are perpendicular to one another (Ishizaki et al., 1997; Sakai et al., 1991). In contrast, the collagen fibrils in the granulation tissue of injured corneas, which have healed for 3 weeks, are no longer assembled in orthogonal lamellae. This disorganized collagen matrix results from remodeling of the injured corneal stroma by degradation and new synthesis (Ishizaki et al., 1997; Sakai et al., 1991). The reason why the tissue remodeling fails to regenerate an orthogonal collagen lamella in healing stroma remains elusive.

Cellularity in Injured Corneas

Epithelial debridement causes keratocytes to undergo apoptosis as discussed above (Gao et al., 1997; Ishizaki et al., 1995; Wilson, 1997; Wilson et al., 1996a) and activate the surrounding keratocytes that are responsible for the repair of stromal wounds (Ishizaki et al., 1993a, 1994, 1997; Jester et al., 1994; Kao et al., 1996b; Moller-Pedersen et al., 1997; Sakai et al., 1991). Although there are no direct experimental data available, it is likely that similar regulatory mechanism may modulate cellularity during PRK wound healing.

The histological examination of lacerated corneas indicated that PMN accumulated within the fibrin plug of the wounds 1 day after injury and were no longer seen after 3 days. Fibroblasts appeared in the fibrin plug at day 7 (Katakami et al., 1988). Initially, keratocytes in normal stromas of injured corneas were not actively engaged in proliferation. At day 3 and day 5, many keratocytes within the stroma adjacent to the wound synthesized DNA as detected by the incorporation of [^{3}H]thymidine using radioautography. At day 7, proliferating fibroblastlike cells were found in the fibrin plugs instead of the stromas, suggesting that the cells within the stroma migrated into the wounds.

Alkali burn causes necrosis in stroma. As the injured corneas heal, the keratocytes proliferate and invade the acellular stroma (Ishizaki et al., 1997). The number of myofibroblasts in granulation tissues increased and peaked within 3 weeks of injury and then declined (Ishizaki et al., 1993a, 1994; Jester et al., 1994). Electron microscopy revealed that some fibroblastic cells in the lacerated cornea, which had healed for 4 weeks, contained dense chromatins. Use of terminal nucleotide TUNEL reveals that some of the fibroblastic cells undergo apoptosis (Ishizaki et al., 1994) and an increased number of fibroblastic cells in granulation tissues undergoes apoptosis when the injured corneas have healed for more than 3 weeks. This increase in apoptotic cells is accompanied by a decrease in the number of proliferative cells as detected by the incorporation of BrdU (Arar et al., 1994; Ishizaki et al., 1995). DNA isolated from alkali-burned corneas, which had healed for 4 weeks, showed the characteristic 200 base pair ladder fragments. These observations indicate that apoptosis serves as a mechanism for the reduction of myofibroblasts during the maturation of granulation tissues in injured corneas.

Aberrant Expression of Cytoskeleton Component

Wound contraction is a common phenomenon in the healing of skin injuries. Contraction of granulation tissues would profoundly affect the collagenous matrix (e.g., collagen fibril spacings) (Majno et al., 1971; Wehland et al., 1980). Recently, it has been suggested that corneal scar tissues contract (Garana et al., 1992; Jester et al., 1994). The expression of contractile protein (i.e., -smooth muscle actin [-SMA]) has been noted in the myofibroblasts of skin and cornea granulation tissues. In stromal granulation tissues, the activated fibroblastic cells or myofibroblasts express characteristic molecules (i.e., adherens molecules [vinculin and talin]) and cellular fibronectin that are involved in

cellular locomotion. Antibodies against cellular fibronectin, vinculin, and talin react with the fibroblastic cells in the injured corneas, but not with the keratocytes of normal corneas (Ishizaki et al., 1994).   Examination with transmission electron microscopy demonstrated the presence of microtendon and fibronexus associated with fibroblastic cells and the presence of stress fiber within fibroblastic cells. The results indicate that the fibroblastic cells are capable of causing the contraction of corneal granulation tissues and alter the collagen fibril spacings. It has been demonstrated that stromal wounds also contract. This may account in part for cornea haze that is due to the formation of opaque scar tissues during PRK wound healing.

Aberrant Expression of Collagen IV by Stromal Fibroblasts in Injured Corneas

In addition to the expression fibril collagen I and V, the stromal fibroblasts of alkali-burned and lacerated corneas that had healed for 1, 7, 21, and 45 days also express collagen IV. This was demonstrated by the use of immunohistochemical studies with goat anticollagen IV antibodies at light and electron microscopy and *in situ* hybridization with an antisense digoxigenin-labeled riboprobe of collagen   1(IV) mRNA. In contrast, 20-day-old fetal corneal stroma was not labeled by the anticollagen IV antibodies, whereas, 1 week after injury specific collagen IV immunostaining was detected in the injured stroma (Ishizaki et al., 1997). As the injured corneas healed, the antibodies reacted with fibroblastic cells and the extracellular matrix of granulation tissues located in the anterior portion of alkali-burned corneas, as well as the posterior portion of lacerated corneas. The middle stroma was weakly labeled by the anticollagen IV antibodies.   Immunoelectron microscopic study showed that collagen IV and fibronectin were closely associated with the fibroblastic cells.   *In situ* hybridization demonstrated that epithelial, endothelial, and fibroblastic cells in the wounded corneal stroma and retrocorneal membrane expressed   1(IV) mRNA, whereas in normal cornea the expression of   1(IV) mRNA was limited to epithelial and endothelial cells (Ishizaki et al., 1997).

Use of transmission electron microscopy   demonstrated the presence of microtendon and basal laminalike structures in the granulation tissue of injured cornea that was similar to what had been described in the granulation tissues of skin wounds (Ishizaki et al., 1994; Skalli and Gabbiani, 1988).   To examine whether the basal laminalike structure contain components of basement membranes and function as a miniature basement membrane, anticollagen IV and antifibronectin antibodies were used in electron microscopy immunostaining of alkali-burned and lacerated corneas. Electron microscopy immunostaining demonstrates that the basal laminalike structures are labeled by anticollagen IV and antifibronectin antibodies and it is closely associated with fibroblastic cells. The enhanced expression of collagen IV by the fibroblastic cells in the stroma is consistent with the interpretation that they contribute to the formation of basal laminalike structures in granulation tissues of injured corneas. The presence of such a basal laminalike structure can create a microenvironment that partitions the granulation tissue and may interfere with the assembly of collagen fibrils into orthogonal lamellae (Gabbiani et al., 1972; Singer et al., 1984). Possibly, in PRK treated corneas the activated keratocytes may also synthesize a basal laminalike structure that can contribute to the formation of an irregular collagen matrix in scar tissues. In addition, this basal laminalike structure containing fibronectin can serve as a substratum for fibroblasts to migrate in the injured stroma (BenEzra and Foidart, 1981; Farhadian et al., 1995; Fujikawa et al., 1981; Ishizaki et al., 1997; Juhasz et al., 1993; Moller-Pedersen et al., 1997; Singer et al., 1984). The migration of fibroblastic cells may facilitate the wound-healing process, but may also cause wound contraction.

Conclusions

As described above, there is a lack of knowledge in our understanding on PRK wound healing. Clinically, PRK is superior to radial keratotomy. However, it is still difficult, if not impossible, to predict the surgery outcomes of PRK. Like the healing of other types of corneal injuries, opaque scar tissues do form in PRK-treated corneas. In addition, regression takes place as a result of stromal wound healing. We know very little about the mechanism of collagen fibrillogenesis during wound healing that result in the formation of a disorganized extracellular matrix in the scar tissues. The consequence of incomplete regeneration of epithelial basement membrane remains unknown. Furthermore, the effect on corneal epithelial cell and keratocyte interaction is unknown but may possibly produce profound adverse and unknown effects.   Clearly, more research is needed to elucidate these possibilities.

The panel recommends that basic studies be conducted to determine the cellular and molecular basis for regulation of collagen fibrillogenesis during repair. In addition, basic studies are needed to identify the regulatory role of the basement membrane in directing epithelial and keratocyte differentiation and function.

CORNEAL ENDOTHELIUM

In rabbit studies, PRK has been shown to alter the corneal endothelium producing enlargement of the endothelial mitochondria and the deposition of an electron-dense fibrillogranular deposit within Descemet's membrane (Sano et al., 1996).   These responses are similar to those obtained after mechanical epithelial abrasion (Hanna et al., 1989) and therefore are not necessarily specific to PRK. Under *in vitro* conditions, endothelial damage and cell loss may also be demonstrated (Lambert et al., 1996); however, the double stress of excimer PRK combined with tissue excision and organ culture may have produced confounding results. In clinical studies using specular microscopy to evaluate corneal endothelial cell density, no change in the central endothelial cells have been demonstrated (Carones et al., 1995; Isager et al., 1996; Trocme et al., 1996). Any changes that were detected appear to be related to the discontinuance of contact lens wear (Trocme et al., 1996) and hence represent a beneficial effect.

Little is known about the effects of LASIK on the corneal endothelium. There is some concern that LASIK may effect the endothelium adversely, particularly because LASIK produces considerably deeper injury that may approach within 100 μm of Descemet's membrane. The Panel recommends that basic studies be conducted to further evaluate and define this risk.

SUMMARY AND RECOMMENDATIONS

Concerning the efficacy of PRK, the wound-healing responses in animal studies from rabbits and primates indicate that the PRK wounds heal predominantly by corneal fibrosis during the first 6 months after surgery. This leads to a complete regression of the refractive effect of PRK in test animals. Based on our knowledge of human healing patterns following radial keratotomy, we would suspect that healing following PRK is considerably delayed and may require up to 3 years to be initiated and perhaps 5 to 10 years or longer to be completed in some patients.   While the physiologic effects of delayed wound healing are unknown, delayed healing in Radial Keratotomy has led to biomechanical weakening of the cornea and the development of hyperopic shifts in a

subset of patients with a higher number of, and more centrally placed, incisions. Although a similar mechanical effect following PRK is not likely, due to the abrasive rather than incisional nature of the injury, the long term consequences of PRK and its effect on mechanical stability, corneal physiology and refractive stability remain a major concern that needs further study. Current clinical studies reporting results from 6-months and 1-year follow-ups are inadequate and do not assess the full potential of PRK to undergo considerable regression. In addition, clinical studies generally are performed on older individuals who are known to show less aggressive healing responses and undergo less regression. The military population at risk may be considerably younger, (i.e., in their twenties, and they should experience more exuberant healing and greater regression. Also, women of child-bearing age are at greater risk for regression during pregnancy, another concern for the military population.

Concerning the safety of PRK, incomplete regeneration of the epithelial basement membrane in animal studies is a major concern. The long-term effect of an abnormal basement membrane on epithelial and stromal differentiation and function is not known, and the potential risk for infection and epithelial erosion needs to be seriously considered. In addition, corneal wounds that remove the basement membrane heal by stromal fibrosis with deeper injuries, producing greater fibrosis. The presence of corneal fibrosis will clearly effect corneal transparency; the long-term clinical significance is not known. Furthermore, the safety of LASIK surgery is completely unknown.

Concerning predictability, differences in corneal hydration between patients makes it unlikely that the accuracy of PRK correction can ever be much better than +1 diopter. Of course that does not take into account the effect of regression that is variable dependent on patient age, sex, and health.

The Panel recommends that any future studies sponsored by the DoD related to corneal and ocular physiology be directed toward answering the following questions:

1. What is the precise *in vivo* decrease in corneal thichness after PRK in patients, and how does achieved photoablation correlate with intended correction?

2. What is the risk for the development of early cataract following single and multiple PRK procedures?

3. What is the tolerance of the cornea to shear stresses after LASIK surgery?

4. What is the depth of injury to underlying cells—keratocytes, and endothelial cells—in patients, and how does the depth of injury correlate with the development of haze and regression?

5. What is corneal haze, how can it be measured objectively, and how does it correlate with visual outcomes including glare and low-contrast visual acuity?

6. What is the risk of UV and solar radiation to haze and regression?

7. What is the cause of regression in patients—epithelial hyperplasia or fibrosis—and how long does it take to stabilize–5 years to 10 years?

8. What is the effect of preganancy and menopause on PRK?

9. Can growth factors or cytokines alter the post-PRK repair process?

10. What is the early inflammatory response and how does it correlate with haze and regression?

11. What is the mechanism of collagen fibrillogenesis and how does it relate to corneal haze?

12. What is the importance of an abnormal basement membrane? Is there any effect on long-term epithelial and keratocyte differentiation, and functions and what is the risk to later infection?

13. What is the risk of corneal endothelial damage following LASIK?

14. What is the risk of corneal anesthesia following PRK, and how does reinnervation modulate epithelial healing and long-lasting epithelial defects after PRK?

How does corneal anesthesia affect basal tear secretion and subsequent corneal drying and damage?

Clinical Ophthalmology and Optometry

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INTRODUCTION

The U.S. Department of Defense has many reasons to explore the application of refractive surgery to military members. Maintenance of normal visual functioning over a career lifetime is essential to preserve the fighting force. Widespread use of refractive surgery in the civilian population will reduce the pool of available recruits for enlistment and commissioning. Eyeglasses and contact lenses may be incompatible with newer technological devices such as night vision headgear or with the environments in which military operations are conducted. Widespread use of eye armor has been, in part, not achieved because of incompatibility with glasses.

Because large amounts of time and resources are initially invested in the training and skill maintenance of essential military personnel, loss of these trained individuals from increasing refractive errors with aging represents a highly undesirable burden on force effectiveness and conservation. Specifically, standard optical devices (glasses, contact lenses) are often inadequate to correct vision in myopic (nearsighted) personnel such as Navy SEALs who have wide operational demands, including diving, parachuting, and swimming. In addition, infantrymen have difficulty functioning in sandy, muddy, or marshy terrain which makes hygienic maintenance of contact lenses or retention of glasses problematical. With increasing risk for potential chemical or biological weapon use in future conflicts, simplified goggle or mask designs may be physically incompatible with glasses or contact lenses or, at the least, require specialized gear for individuals that would greatly exacerbate long-range logistics costs. Therefore, a safe and effective refractive surgical procedure with permanent and predictable visual results that could profoundly enhance force performance and conservation at a decreased long-term cost would be very desirable. However, surgical treatment of eye refractive errors has been almost exclusively restricted to correction of myopia (nearsightedness) and often co-associated astigmatism. Surgical techniques for the surgical correction of hyperopia (farsightedness) are at a very early stage of development; therefore in this chapter we confine our discussion to a review of surgical laser treatment of myopia/myopic astigmatism that has been approved by the FDA and now is in widespread use among the general public in the United States and around the world.

The oldest refractive surgical method to correct myopia is radial keratotomy (RK). First described in the 1800s and advocated in the late 1970s, RK was widely used in the United States and around the world in the 1980s. An excellent 10-year follow-up study on the long-term safety and efficacy of RK was funded by the National Eye Institute which revealed significant limitations in both initial efficacy and long-term safety (Waring, 1995). Wisely, the military community did not adopt this procedure because of (1) poor overall predictability above 4.00 diopters of myopia, limiting the

usefulness of the method; (2) inaccurate or absent astigmatic correction; and (3) significant side effects of glare or starburst effects, fluctuating vision not correctable by glasses, instability at high altitudes, subsequent contact lens intolerance, severe weakening of the cornea (full depth incisions used) that make traumatic ocular rupture possible in combat conditions and an unfortunate progressive effect in >40 percent of individuals at 10 years, which eventually may produce hyperopia (farsightedness).

By contrast, the introduction of surface corneal laser ablation using a 193-nm excimer laser to sculpt an individual patient's myopic or astigmatic correction permanently into the central surface of the cornea has now become the worldwide standard surgical procedure for correction of low myopic and astigmatic refractive disorders. PRK requires several steps to complete: (1) epithelium is removed mechanically, chemically assisted, or with the laser in the central 6.5–7.0 mm; (2) the patient is aligned beneath the laser head with a fixation light; (3) under computer control, the "cold laser" beam is applied to the cornea, removing both a predictable pattern and volume of tissue (15–180 seconds); (4) patching or bandage contact lens is used until the epithelium heals (3–4 days). In addition to the precision of PRK is the lack of "collateral tissue damage" outside of the photoablated areas, which is a unique feature of the "cold" excimer wavelength energy utilized. Following nearly a decade of clinical investigation, the FDA-approved and widespread use of this technology is now an important part of conventional eye surgery practiced in the United States and around the world, with excellent acceptance by the public and visual care professionals in both optometry and ophthalmology.

PRK is done by excimer lasers (typically Ar-F) using broad-beam or scanning (slit or spot) technologies. The shape of the ablation zone is altered by blocking the 7-mm broad beam with a mechanical iris, other device, or an ablatable material. Shape of the scanning laser ablation is determined by the pattern created with the 1–2-mm spot or varying shaped slit. Excimer lasers are relatively low frequency (5–50 Hz) but high energy (160–180 mJ). The other technology to achieve PRK are the flying-spot lasers. These are solid state and achieve ablation patterns by moving a very small beam (0.25–1.0 mm) of low energy (100–120 mjoules) at high rates (500–1000 Hz) which require an active eye-tracking mechanism. Only broad-beam excimer technology has been approved by the FDA. Scanning excimer and flying-spot lasers have potential advantages over broad-beam lasers, including versatility, smoother ablations, and durability, but no studies have compared the technologies in a controlled manner.

Newer types of refractive surgery for myopia and hyperopia are also emerging but are much less widely studied for efficacy and safety. These include

1. LASIK (laser-assisted *in situ* keratomileusis)
2. intracorneal devices
   a. Circular rings or ring segments
   b. Plastic lenses
3. intraocular lenses

Published high-quality data are insufficient at this time to support informed judgment on the safety or efficacy of these newer developments. LASIK is sufficiently promising, and should continue to be studied in a military setting (see below).

In the following sections of this chapter we discuss in detail the case for and against the introduction of PRK and LASIK to correct myopia and/or associated astigmatism in military personnel.

PRK VERSUS LASIK: QUESTIONS AND ISSUES

There are five basic clinical questions to be considered in assessing the potential positive and negative impacts on use of PRK and LASIK in military personnel:

1. Who is eligible? (recruitment/retention?)
2. What is the efficacy of the procedure in correcting myopia and astigmatism?
3. What are the short- and long-term safety issues of the procedure?
4. What are the limitations of treated personnel? What are job performance requirements and limitations? What are environmental limitations?
5. What is the best current technology and treatment technique?

Eligibility

All patients over 21 years of age with normal eye examinations (except for refractive myopia and astigmatism of the appropriate ranges) are currently eligible, except for pregnant, potentially pregnant, or lactating females. Pregnancy and lactation are associated with a currently unexplained variable regression of PRK treatment effect. Pregnancy should be avoided for at least 1 year after treatment. Postmenopausal women may experience a similar effect, but conflicting reports exist.

Specific pre-existing medical exclusions include history of ocular herpes, severe dry eyes, and other conditions associated with poor corneal wound healing such as diabetes, keratoconus, irregular astigmatism, rheumatoid arthritis, and autoimmune conditions involving collagen. VISX also excludes patients taking Accutane (trademark) or amiodarone (generic).

Specific refractive limits have been established by the FDA and the published medical literature. In general, treatment of under -1.00 diopters of myopia is inadvisable because of the possibility of overcorrection, and correction of myopia above -7.00 diopters with existing approved technology shows significantly decreased predictability and stability. The VISX Star laser is approved by the FDA for -1.00 to -6.00 spherical myopia and up to 4.00 diopters of associated myopic astigmatic cylinder. The Summit laser is approved for spherical myopia from –1.50 to –7.00 diopters. In the absence of large, controlled peer-reviewed clinical trials, FDA guidelines should be followed for any other manufacturers' equipment as they are approved. Refractive stability must be established by demonstrating no more than 1.00-diopter change in refraction over the prior 2 years (0.50 diopters per year). Corneal topography should exclude corneal dystrophies (keratoconus) and significant irregular astigmatism (as from contact lens wear) prior to PRK.

Efficacy

Patients seek PRK to reduce or eliminate the need for corrective distance glasses or contact lenses. Unfortunately, no published study of PRK provides any useful measure of residual spectacle or contact lens use *(research requirement 3-1).* However, this can be estimated routinely by measurements of Snellen Chart Visual acuity. In general, patients with uncorrected acuity of <20/40 may be eyeglass independent; most states do not require eyeglass or contact lens correction for drivers licenses if vision is 20/40 or better uncorrected. Prospective Evaluation of Radial Keratotomy (PERK) data shows that with 20/20 or better in one or both eyes, 77 percent do not wear glasses for distance; from 20/25 to 20/40, 34 percent do not wear glasses for distance; with less than 20/40, 13 percent do not wear glasses (Bourque, 1994). In this volume we assume that uncorrected distance acuity of 20/40 or better will represent a desirable result.

Although there are carefully documented 1–5-year follow-up results after PRK, and these studies report no serious intermediate-term problems of stability of refractive results after 1 year, it must be understood that the long-term results for stability and efficacy need to be established in both military and civilian populations. Clearly, there is a compelling need for each military service component to establish individual task performance standards and testing other than Snellen visual acuity to compare pre-PRK performance scores using glasses or contact lenses for correction with post-PRK results*(research requirement 3-2)*. Although healing of the epithelium occurs in 3–4 days, there are no data on how rapidly people return to work following PRK *(research requirement 3-3)*.

The second measure of efficacy is residual refractive error of ±0.50 diopters. PERK data showed that 85 percent corrected to within ±.50 diopters did not wear distance glasses. With a residual error of ±1.00 diopters, the rate of no distance glasses drops to 39 percent (Bourque, 1994). The results following PRK are not published, but preliminary rates of no glasses can be obtained from Schallhorn's unpublished data (1997a). Many qualifiers are needed because young (<40-year-old) patients who have residual hyperopia may accommodate to see without glasses, and patients older than 40 will typically need reading glasses with any procedure. Postoperative corneal contour and daily fluctuations make the RK data inadequate in estimating the no-glasses rate following PRK.

PRK Safety and Problems

PRK displays the following significant potential problems and complications that may cause transient or permanent loss of two or more lines of pre-treatment, best spectacle-corrected visual acuity (BSCVA):

1. corneal haze associated with increased halos, glare (worse at night);
2. corneal infection;
3. post-PRK contact lens intolerance for residual under- or overcorrections;
4. cataract or glaucoma if corticosteroids are used in the postoperative period;
5. prolonged visual recovery to best acuity levels (up to 1 year);
6. under or overcorrection by more than ±1.00 diopters;
7. regression of treatment effect;
8. irregular surface astigmatism with reduced vision;
9. recurrent erosion of the healed corneal epithelium;
10. treatment technical problems: beam decentration or "central islands" of unablated tissue; and
11. loss of low-contrast visual sensitivity with potential task-specific negative impact (not as yet demonstrated for any military performance demand, e.g., night driving, night goggle use, vision in foggy or smoking environments, etc.).

Of these potential clinical problems, three are paramount as a potential impact on military needs:

1. length of time to recovery of best, stable vision *(research requirement 3-4)*;
2. permanent loss of two or more lines of visual acuity; and
3. assessment of impact of post-PRK night vision/low-contrast sensitivity performance *(research requirement 3-5)*.

The other problems, although potentially serious, are extremely rare, transient, or avoidable (islands, decentered ablations) by newer laser model technologies with improved software and ablative nomograms (power settings optimized for individual

corrections). Again, although long-term results (10 years) are not yet available for PRK, 1–5-year data do not suggest significantly increasing future problems.

Limitations

There is a rare late onset of haze and regression attributed to UV radiation exposure in the first year after PRK. Therefore, it may be necessary for military personnel to either avoid high-UV environmental conditions or wear UV protection. UV protection could easily be placed into standard military devices by appropriate coatings and should not be a significant problem.

Pregnancy in females within 1 year of PRK may result in severe regression of treatment effects and should be discouraged.

Reduced low-contrast visual acuity may interfere with vision in special circumstances of night vision, target acquisition in dusty or smoky environments, or other low-light circumstances. This research requirement is discussed in Chapter 4.

Best Technology

Currently, only two companies have received FDA approval for laser sales in the United States: Summit Technologies and the VISX Corporation. Of these, only VISX is currently approved by the FDA to correct both astigmatism and myopia. Although use of newer generations of lasers is under clinical investigation (see the results of the Autonomous laser in the next section) and may provide improved results, there are insufficient data at this time to assess safety and efficacy of these devices. Therefore, results evaluated in this volume are largely confined to FDA-approved lasers, although additional information is provided to allow the reader to compare the future potential of devices and procedures that are under development with currently established procedures and machines. The following companies have submitted data to the FDA, but the complete data packets were not available for review: (1) Autonomous Technologies LADARVision (scanning spot for low myopia, astigmatism and high myopia) which is undergoing FDA review; (2) Nidek EC-5000 (low myopia and high myopia); (3) Chiron-Technolas Keracor (low and high myopia and astigmatism), which was bought by Bausch & Lomb during the course of this study and may be renamed; (4) Summit Apex Plus (high myopia, astigmatism and LASIK); and (5) VISX Star (high myopia) (DuBosar, 1998).

There are several areas of newer technology and treatment methods that are now being studied by the clinical research community that may lead to significantly improved visual results:

1.   Removal of surface corneal epithelium by laser (laserscrape) or alcohol-assisted methods versus the older method of mechanical removal with spatula or blade, originally approved by the FDA.

2. Use of a soft therapeutic bandage contact lens to speed up epithelial healing for 3–5 days post-PRK (generally accepted).

3. Changing the ablation profile to use multipass, multizone techniques. These may increase the accuracy and decrease side effects of haze, glare, halos and loss of BSCVA.

4. Performance of PRK in the middle of the cornea under a thin corneal flap made by a mechanical cutting device. When PRK is done in this way it is called LASIK.

It should be understood that the laser treatment portion of the LASIK surgery is the same as for ordinary PRK, although power settings may differ (nomogram will vary by surgeon, equipment, and location), and , most important, the best visual results (1–3 months) are determined by the laser and not by the flap. The advantages of doing PRK under a corneal flap, (LASIK), are rapid visual recovery (1–2 days), less haze (especially in higher myopes), fewer postoperative medications for a shorter time, less postoperative pain, and the possibility of bilateral surgery at one sitting. Unfortunately, there is a serious potential for flap-associated complications (1–5 percent) which can have severe, sight-threatening implications. Thus, with LASIK, decreased rehabilitation time is associated with a potentially increased overall risk of permanent visual loss. Current visual results are also less with LASIK; however, this is improving over time as new laser nomograms evolve.

There is also a serious question of flap healing. After LASIK, the cornea may never truly restore pretreatment mechanical stability and the ability to withstand the possibility of tolerating severe trauma, blast forces, G-forces, or hyperbaric environments commonly encountered in military environments *(research requirement 3-6)* ; refractive stability in hyper/hypobaric conditions *(research requirement 3-7)*; and resistance to sheer forces in an animal model following LASIK.

In the next section we provide a summary of the best published medical data, which are necessary to assess the efficacy and safety of PRK at this time in the general and military populations.

CURRENT KNOWLEDGE

Current published data are based on a small fraction of all PRK procedures performed and they represent a minimal case scenario. Peer-reviewed data lag clinical experience by 2–3 years. None of the published series of data include a control group who does not receive surgery. Very few of the large series reflect current equipment and practice and most do not have even a 90 percent follow-up rate at 1 year and longer. The best reports have generally less than 50 eyes. We have used only larger reports that have some form of peer review in compiling our study. Many times rare and unusual problems will not be seen in the early FDA reports, but will accrue with postmarketing surveillance. Current FDA-suggested guidelines for an Investigational Device Exemption are found in the *Journal of Refractive Surgery* 13:579–587, 1997. These guidelines comprise the data typically used by the FDA in determining safety and efficacy prior to granting a premarket approval to a manufacturer.

Efficacy

Results for efficacy are summarized in Chapter 4. As noted above, efficacy is best judged by the percentage of patients who do not require refractive aids for visual function after surgery. The one report for PRK in one or both eyes is in a chapter by McDonald MB and Chitkara (1997). VISX determined that 89.8 percent of 701 enrollees used corrective eyewear before PRK. At 1 year, 10.1 percent of 310 patients still used corrective eyewear. No description of the age of patients or correlation to near versus distance correction was given.

Substitute efficacy measures include the percentage of patients achieving 20/20 and 20/40 uncorrected acuity and the percentage of patients with residual refractive

error of ±0.50 and ±1.00 diopters. Table 3-1 lists, by equipment, studies that have a minimum of 75 eyes and a follow-up of 12 months for the low to moderate myopes. Most of these eyes were done with earlier models of VISX (the Twenty/Twenty model) or Summit (Omnimed model) which are no longer available. It is assumed that these results can be generalized to the later and improved models. FDA approval for Summit to use a 6.0-mm optical (ablation) zone was based on a subset of data that is not available.

Table 3-1. Efficacy of PRK in Low to Moderate Myopia

Corpora-tion	Study	Eyes	Follow up	UCVA (percent 20/20)	UCVA (percent 20/40)	±0.50 diopter (percent)	±1.00 diopter (percent)
VISX	VISX group	521	12 months	50	88	48	78
	McCarty, 1996 (6.0 AZ)	273	12 months	47	87	ND	87
	Snibson, 1995	107	12 months	46	88	ND	89
	VISX training manual	280	24 months	58.3	93.7	64.5	90.2
Summit	Summit group	585	12 months	66.4	90.7	58.0	77.7
	Hersh, 1997 (4.5, 5.0 AZ)	612	24 months	66.5	92.5	54.9	77.8
	Halliday, 1995 (5.0 AZ)	82	12 months	49	79	59	79
Autono-mous	FDA-U.S.	187	6 months	72	96	84	95
	FDA-Greece	93	12 months	70	99	80	91

Notes: UCVA, uncorrected visual acuity; AZ, ablation-zone diameter, in mm; ND, not done. Source: McDonald MB and Chitkara (1997).

Time to return of BSCVA is not published. Time off work and time to return to full visual performance are not published but may be estimated.   Time off work is estimated from time to re-epithelialize, which ranges from 2 to 7 days with the mean at approximately 3.2 days. Time to return to full visual performance can be estimated from time to return to preoperative BSCVA and time to visual stability (<1- diopter change). First measurements were generally at 1 month with relative stability occurring at 3–6 months. Most data are reported as means without scatter diagrams which may mask late instability in a subset of patients.

In a small percentage of patients, BSCVA can be enhanced, and this may potentially improve military performance. Until there is a good measure of military performance, the advantage of improving BSCVA cannot be determined.

In assessing the efficacy of PRK, for military application, a large potential pool of civilians exists in the numerous police officers, fire fighters, paramedic, and Federal Aviation Administration pilots who have had RK, PRK or LASIK. An epidemiological study could be designed to survey the experience of the agencies who have approved

these procedures for their professionals to determine what, if any, negative and positive impacts have occurred *(research requirement 3-8)*.

Safety

Safety is determined from the frequency and severity of complications. In the small series of date (<1000 eyes) that are published, rare or unusual complications will not be detected. The best overall evaluation of safety comes from measuring the frequency of loss of two or more lines of BSCVA. Physiologic variation in BSCVA has not been studied. Change in best corrected visual acuity with contact lenses may be a better standard but has not been studied in part because many patients seeking refractive surgery are unable to use contact lenses. In this range of myopia, a magnification effect from surgery would lead to an average of two letters increase in visual acuity (five letters per line); therefore, the expectation is no change or a one-line improvement in BSCVA. One-line variation is accepted as within normal variation (from FDA standards). Therefore two-line loss of BSCVA is significant. Table 3-2 summarizes this safety data.

Table 3-2. Loss of vision (BSCVA) with PRK

Corpora-tion	Study	Eyes	Follow up	Loss of 2 Lines BSCVA at 6 Months (percent)	Loss of 2 Lines BSCVA at 12 Months (percent)	Final BSCVA <20/20 (percent)
VISX	VISX group[( ]	521	12 months	NA	1.5	NA
	McCarty, 1996 (6.0 AZ)	273	12 months	NA	4	NA
	Snibson, 1995	107	12 months	NA	6	4
	VISX training manual	328	24 months	2.3	2.2	1.3
Summit	Summit group	585	12 months	NA	3.1	2.8
	Hersh, 1997 (4.5, 5.0 AZ)	612	24 months	3.1	2.9	3.1
	Halliday, 1995 (5.0 AZ)	82	12 months	NA	16.4	NA
Autono-mous	FDA-U.S.	187	6 months	0	NA	0
	FDA-Greece	93	12 months	0	0	0

Notes: AZ, ablation-zone diameter; NA, not available.
Source: McDonald and Chigkara (1997).

VISX data regarding loss of two lines of BSCVA have improved to 0 percent in subsequent trials with the deletion of the nitrogen blow-by in the later studies. The VISX

training manual indicates reduction in loss of BSCVA of two or more lines to 0.3% at 24 months (see also Table 3-2). Loss of BSCVA may be due to irregular astigmatism, cataract, retinal disease, or corneal scarring. The Summit data for 2 years (not in table) indicated a 7.9 percent loss of BSCVA. For final approval an additional 500 patients were evaluated, and the rate must have been below 5 percent, if the FDA-conditional approval was completed. Most studies show a reduction in the percentage of patients with a loss of two or more lines BSCVA between 1 month and 1 year. The O'Brart study (1995) showed a rate of 15 percent loss of three lines BSCVA with 5.0-mm absolute-zero diameter versus 0 percent with 6.0-mm absolute-zero diameter using the Omnimed. Loss of two lines was not reported. Brancato (1993) in a Summit study with Omnimed reported 1.4 percent two-line loss of BSCVA. Even more important, especially with low myopia, many patients that have BSCVA 20/20+ preoperatively do not have at least 20/20 postoperatively. No study reports the data in this format, but it is available in the FDA studies as reported by McDonald and Chitkara (1997) and the VISX training manual, as shown in Table 3-2 *(research requirement 3-9)*.

Improvement in this measure of safety is shown with newer technologies as evidenced by the Autonomous data and the later VISX data. This may not be the best measure of safety because significant numbers of patients (3.5 percent with VISX and 19.7 percent with Summit FDA data) showed better than one line of improvement in the BSCVA. Both safety and efficacy improve with subsequent algorithms developed by the manufacturers. No PRK study showed a variation by surgeon experience or age of patients. Both safety and efficacy by these measures show an increase variation from desired treatment with increasing loss of BSCVA in higher myopia (generally above 7.00 diopters).

A loss of contrast sensitivity is related to loss of BSCVA as discussed in Chapter 4. Few studies have described loss of contrast sensitivity following PRK, and no standard test or testing condition exists. Seiler and McDonnell (1995) summarize the different studies and indicate an initial reduction in contrast sensitivity following PRK that generally returns in 3–12 months. This reduction occurs even in the absence of corneal scarring. However, there is a reduction in low light, low-contrast testing (described in Chapter 4) that is associated with diminished performance in night driving testing. Night driving testing needs further evaluation for both public health concerns and potential military applications such as target detection in low-contrast environments. It may be possible to test this using newer driving simulators (such as those at the University of Iowa and University of Maryland) or with the Mesoptometer as used in Germany and proposed for use by CDR Schallhorn. As before, these tests need to be correlated to specific military requirements *(research requirement 3-10)*.

Stability

Instability in RK was not recognized in the 1–2 year PERK study, but became clear at 5 years and was increasing at 10 years. Population studies support a rapid increase of myopia to approximately age 18, then a slow increase in myopia to age 45, followed by a shift to increase in hyperopia thereafter (Ellingsen, 1997). No studies include a group controlling for this change in population mean. To date, no study has shown a progression of effect with PRK (or LASIK) from 1 month to as long as 5 years. A small subset in the Summit Phase III trial showed hyperopic shift of +0.50 diopters from 18 to 24 months in 8 percent and +1.00 diopters in 1.9 percent (Hersh et al., 1997). Ninety-six percent were stable within 1 diopter.

Published information at 12 months post-PRK support stability at 3 months, but with wide variation, as shown in Table 3-3. No study looks at patterns of stability (i.e., subsets of patients who continue to change). Durrie et al. (1995) showed three patterns of healing—normal, inadequate, and aggressive. He suggested a

difference in rates of regression with the aggressive healers showing more. He could not classify the patients prior to surgery (this topic is discussed in more detail in Chapter 2). Two studies show 3- and 5-year data (Hamberg-Nyström et al., 1996 and Kim, 1997). Using Summit with a small ablation zone (4.5 to 5.0), Hamberg-Nyström et al. showed stability between 24 and 36 months for 457 eyes. With only 10 percent follow-up in a study of 201 eyes, Kim showed a myopic regression from –1.36 ± 1.35 to –2.43 ± 1.90 from 1 year to 5 years post-PRK in a group with mean preoperative refraction of –6.98 ± 2.77 using the VISX laser. Using a 4.0 mm ablation zone with the Summit laser, Stephenson, et al. (1998) showed no further regression after 1 year in 83 patients (representing 68 percent follow-up) examined at 6 years post-operatively. They also showed no hyperopic drift, diurnal fluctuation, or intraocular complications. Longer studies with more complete follow up need to be undertaken *(research requirement 3-11)*.

Table 3-3. Mean Refracted Error by Month

Corpora-tion	Study	Pre-operative	Month 1	Month 3	Month 6	Month 12	Month 24
VISX	VISX group	-3.8				-0.25	
	McCarty, 1996 (6.0 AZ)	-3.47±1.13	See Figure 3-1				
	Snibson, 1995	-3.42±1.03	+0.23±0.79	-0.26±0.62	-0.28±0.46	-0.27±0.51	
	VISX training manual	4.07±0.23	0.08±0.15	-0.19±0.08	0.26±0.12	-0.24±0.07	0.34±0.07
Summit	Summit group	-4. 2					
	Hersh, 1997 (4.5, 5.0 AZ)	-4.42	+1.58±1.16	+0.75±1.02	+0.35±1.03	+0.06±1.02	-0.08±1.04
	Halliday, 1995 (5.0 AZ)						
Auton-omous	FDA-U.S.	-4.00±1.88	+0.33±0.77	0.00±0.45	-0.17±0.43		
	FDA-Greece	-4.24±1.20	+0.51±0.80	0.05±0.61	0.00±0.56	0.00±0.60	

Source: McDonald and Chotkara (1997). Seiler and McDonnell (1995) include many more references with widely varying preoperative myopia, length of follow-up, and number of eyes.

Complications

Quantifying complications in general require a very large series of data. Best estimates of frequency are summarized in Seiler and McDonnell (1995) and are noted below.

1. Undercorrections occur in two basic manners: insufficient initial treatment and regression of effect over time.

(a) Initial undercorrections are generally determined at 3 months and, if stable, reoperated at 6 months. Rates of undercorrection of 1 or more diopters range

from <1 percent in recent studies to 10 percent in the initial FDA trials (10.2 percent retreatments with VISX and 3.4 percent with Summit). Not all undercorrections are retreated because some patients may adapt to monovision (one eye for near, one for distance) or they may not like the side effects of the operation. Rates of undercorrection increase with increasing myopia (McCarty, 1996; Taylor, 1996).

Reoperations are successful (residual error within ±1.00 diopters) 60 percent (Seiler, 1992) to 100 percent (Schallhorn, 1997c) of cases. Chaterjee (1997) reported reduction in preoperative residual myopia of 164 patients from a mean of –2.59±1.36 (range –0.50 to –7.75) to –0.52±1.36 (range +2.50 to –5.50.) Patients had 20/20 or 20/40 UCVA at 6 months 25.1 and 66.7 percent of the time. Loss of two lines BSCVA occurred in 6.1 percent (6.8 percent of those treated with Nidek EC-5000 laser and 0.0 percent treated with Summit). All corneas had less than grade 1 haze. Snibson (1996) reported retreatment in 48 eyes, 5 of which had been < -5.00 diopters before the original treatment and the rest up to –15.00 diopters. This study compared retreatments with the original group and found 69 percent versus 75 percent within ±1.00 diopter and 64 percent versus 76 percent 20/40 or better uncorrected visual acuity (UCVA). There was no difference in the adverse reaction profile between the groups. Only three corneas had significant haze, but some eyes were treated for central islands, confounding the analysis of these results.

(b) Regression of initial effect is poorly understood (see Chapter 2). Long attributed to thickening and remodeling of the epithelium, animal data and now human data (Moller-Pedersen, 1997; Tanzer, 1997) suggest that the epithelium does not thicken with time. Most studies do not separate results of treating an initial undercorrection from that attributed to haze formation. However, current opinion is to delay retreatment in the presence of greater than grade 1 haze for a year or longer to allow stabilization. Regression and undertreatment attributed to central island formation is similarly treated only after assuring long-term stability because most islands will resolve over a year. Corbett et al. (1996b) performed a multivariate analysis of regression in 100 patients demonstrating no relationship with sex of the patient, previous contact lens wear, swimming, smoking, or minor ocular trauma. They found significant correlation with higher dioptric or smaller-diameter treatments, use of oral contraceptives, significant UV light exposure, and ocular surface disorders, but regression was defined as 0.50 change for low myopia (-3) and 2 diopter change in higher myopia (-6). The VISX training manual indicates that 17 of 909 patients were retreated for regression with or without haze by 2 years. Data were presented for all 33 retreatments together (undercorrection in 12, decentered ablation, etc., in 4). Seven percent resulted in better than 20/20 UCVA, and 71.4 percent became 20/40 or better. Fifty percent became ±0.50 and 78.6 percent ±1. These are similar to first-operation eyes but do show an increased risk for second operation that may be related to the patients' healing responses.

2. Overcorrection of more than +1 occurs more frequently in the Summit data sets (12.3 percent versus 4.5 percent) than with VISX in FDA trials. Small amounts of overcorrection may be desired to allow for the mild regression and to give best unaided vision in young (<40-year-old) myopes. At this time there is no approved management for significant overcorrections. Various options, including removal of epithelium, chronic soft contact lens wear, holmium laser thermokeratoplasty, shielded phototherapeutic keratoplasty (PTK) (Buzard, 1997), hyperopic PRK, and hyperopic automated lamellar keratoplasty have been suggested but none are demonstrated to work.

3. Steroid-induced side effects include increased intraocular pressure (IOP), increased cataract formation and increased susceptibility to infection.

(a) Increased IOP occurs in 1.6–25 percent depending on the measure used. Population studies suggest that 3 percent of patients would be genetically susceptible to increased IOP with chronic topical steroid use. Most elevations are reversible by discontinuing the steroid, with only a few reports of temporary antiglaucoma therapy being required, and only one report of eyes requiring trabeculectomy where the rate was 3 of 2920 eyes treated with laser and steroids (Kim and Sah, et al., 1994). Compounding this problem, however, are the recent reports of falsely low readings by the Goldman tonometer following PRK (and possibly LASIK) of approximately 2–4 mmHg (varying with amount of myopia treatment). This topic is discussed in more detail in Chapter 2.
(b) Cataracts may be induced by chronic steroid use, but in general, only with therapy for a year at four times a day. UV radiation scattered at the time of PRK may be cataractogenic, but to date the only reported cataracts have been attributed to normal aging. At least one report of 34 cataracts following PRK is in press, but the denominator of the total number of PRKs done is unknown. Cataract surgery has been successful following PRK.
(c) Bacterial infections occur following PRK with or without the use of bandage contact lenses, and herpes simplex virus has been reported following PRK. Herpes simplex virus may be inducible by the UV light or by the chronic administration of steroids. Known herpes simplex is a contraindication to elective PRK.

4. Haze is the euphemism for central corneal scarring. (Details are provided in Chapters 2 and 4 regarding subjective measurement.) Haze is the backscatter of light from the cornea that may correlate with patient symptoms of glare. Normal corneas have a small amount of haze, but many corneas develop more haze following PRK.

(a) Postoperative haze occurs in 83.4 percent at 1 month, declining to 27.8 percent at 2 years. Mean haze peaks at 1 month with the Summit and begins to decline at 3 months (Hersh et al., 1997). Haze peaks at 1 month with a mean of 0.8 (scale 0 to 4) and declines to 0.2 at 12 months with the VISX. No patients with low myopia had a score greater than 2 at 12 months (McCarty et al., 1996). No patients had more than 0.5 haze with the Autonomous scanning laser at 12 months and 70 percent were clear (Autonomous, 1997). Haze may respond to topical steroids, nonsteroidal anti-inflammatory drugs or antimetabolites, but the data remain inconclusive. Correlation of haze to symptoms of glare and halo is poor. Incidence of haze increases with increased depth of treatment (Taylor, 1996), but decreases with time. Central haze does not seem to occur with LASIK.
        Late onset of haze following a period of clear cornea has been recently reported and seems to have a low incidence (Lipshitz et al., 1997, Chapter 2). The cause is unknown, but may be related to excessive exposure to UV light. It may respond to topical steroids. This haze is also related to deeper ablations.

5. Induced astigmatism developed in 1.4 percent of 825 eyes in Loewenstein et al (1997). The VISX and FDA studies cited above showed no significant induction of refractive or keratometric astigmatism with spherical treatments.

a) Topographic anomalies include irregular astigmatism and central islands. Irregular astigmatism occurs when the corneal refractive power cannot be neutralized with normal spherocylindrical glasses. Visual acuity may improve

with contact lenses. Only rare incidences are documented and no study reports the frequency of irregular astigmatism or contact lens wear after PRK. Unfortunately there is not a generally accepted method of measuring irregular astigmatism, although several computerized corneal topographic instruments have proprietary estimates. Irregular astigmatism may be related to the postoperative, aspheric shape of the cornea discussed in Chapter 4.   Central islands are a topographic anomaly with no accepted universal definition.   In general they occur with broad-beam lasers and may be avoided by pretreatment (manufacturer's nomogram on the VISX, surgeon nomogram on the Summit). Incidence varies with up to 70 percent in one series   (Seiler and McDonnell, 1995). They occur infrequently or never with scanning excimer and flying-spot lasers. They may disappear with time following epithelial or stromal healing and should be treated only if associated with undercorrection or significant haze after stability is achieved.

(b) Decentration of the treatment zone would be expected to alter the refractive results and potentially be associated with other symptoms.   Unfortunately, decentration is difficult to measure. In one study (Doane et al., 1995), 27 patients with less than 0.5-mm decentration (mean 0.30 mm at 190 degrees) were compared with 11 patients with more than 0.5 mm (mean 0.66 mm at 198 degrees). They found no difference in acuity or refractive results and no correlation with glare or night driving symptoms. There was a weak correlation with halo symptoms.

6. Glare is discussed in detail in Chapter 4. Glare occurs prior to PRK with glasses and contact lenses and in emmetropes. Unfortunately there is not a good correlation of this subjective symptom with objective measures, including van den Berg's measure of forward light scatter. Some studies indicate a reduction in glare following PRK, but the results are very variable and indicate improvement with time following surgery.

7. Halos are discussed in Chapter 4. They are related to ablation-zone size and depth of ablation. Their relationship to military performance is unknown.

8. Loss of contrast sensitivity with and without a glare source is discussed in Chapter 4. The key remaining question (see above) is the degree and duration of loss of low-frequency contrast sensitivity following PRK.

9. Infections are estimated to occur in 0.05– 0.2 percent of cases and may be related to the bandage contact lens, nonsteroidal anti-inflammatory drugs and steroids. Bacterial, fungal, protozoal (amebic) and viral infections have been reported (Seiler and McDonnell, 1995; Cuevas and Sutphin, 1998).   Most infections have responded to medical treatment with only one known transplant for infection following PRK. Another case of corneal transplant occurred in a patient with sterile inflammation attributed to systemic lupus erythematosus (Seiler et al., 1994).

10. Sterile corneal infiltrates are associated with bandage contact lenses and topical nonsteroidal anti-inflammatory drug use. They may occur as frequently as 0.5 percent (Seiler and McDonnell, 1995). They are not associated with loss of vision, but infections must be sought and treated appropriately.

11. Recurrent epithelial breakdown symptoms occur in 1– 20 percent of patients, but generally disappear after 6–9 months (Seiler and McDonnell, 1995).   Clinically documented erosion is very rare, but may follow tonometry. Recurrent corneal erosion syndrome can be treated by PTK, implying that PRK should not induce excess incidence of erosions. This is discussed further in Chapter 2.

12. Reduced corneal sensitivity follows PRK, with return to baseline over 3–12 months. This transient decrease may be related to a temporary decline in reflex tearing and could have consequences in low-humidity environments (flight, high altitude). This is discussed further in Chapter 2.

13. Diurnal variation in vision is generally not reported, although there are two studies suggesting it occurs following PRK (Kim, 1993; Seiler, 1992). One explanation suggested decrease hyperopia during the day with no change in autorefractor or keratometry in contrast to RK where there is increasing myopia during the day with changes in those measures. The patients were still hyperopic which may explain the symptoms in the five patients.

14. Retinal complications of choroidal neovascular membrane macular cysts and retinal detachment have been rarely reported, but not at a rate higher than expected for degree of myopia.

15. Endothelial changes are insignificant following PRK of low myopia. If anything, there is improvement in density, pleomorphism, and hexagonality possibly related to discontinuing the use of contact lenses (Carones, 1994).

Astigmatic Results

Tabin, et al (1996) best describe results for astigmatic PRK (PARK or PRKa). In 297 patients with up to -10.00 diopters of spherical error and 6.00 diopters of astigmatism, 38.7 percent were 20/20 or better (UCVA) and 80 percent were 20/40 or better (UCVA). Seventy-four percent were within +/- 1.00. After an adjustment in targeted astigmatism, they were able to correct a geometric mean of 90 percent of astigmatism at 12 months. Variability of axis was greatest for less than 1.00 diopters of astigmatism implying more accurate targeting of higher degrees of astigmatism. Up to 60 percent of low myopes will have an associated astigmatism of 0.75 diopters or more. At this time only myopic astigmatism is approved (sphere of zero or less with minus cylinder).

Results of PARK compared with PRK are available in an even more limited group of papers *(research requirement 3-12)*. Analysis and comparison is difficult because there is no standard for interpreting astigmatic change. Analysis should include amount and direction (vector) preoperatively and postoperatively and the decomposition calculated to provide the cylinder vector induced by the machine. Most analyses give only the absolute amount of cylinder, although an error of only 15 degrees in application reduces the effectiveness 50 percent. In general, safety and efficacy parallel PRK with only the additional complication of under- or overcorrected cylinder.   Analysis of cylinder is discussed by Alpins (1993, 1997). Taylor et al. (1994) best describe the results. In 344 patients, 72 percent had 20/40 UCVA (20/20 data not given) with 84.9 percent of low myopic astigmats ±1 (±0.50 not given). The mean change in astigmatic axis was approximately 0 degrees with a standard deviation of 30 degrees. In absolute terms, they achieved approximately 60 percent reduction in astigmatism at 12 months after an adjustment to the original nomogram.

Autonomous (1997) FDA data in 211 eyes at 3 months showed UCVA of 20/20 or better in 54 percent and 20/40 or better in 91 percent with 72 percent ±0.50 diopters and 91 percent ±1.00 diopters. No patients lost two or more lines of BSCVA. Vector analysis is not described.
The Summit ablatable mask technique may provide a smoother surface with a potentially wider range of corrections, but there is only one recent publication. In that report of only 59 eyes with a 12 month follow-up using the erodible mask technique, astigmatism was reduced from 2.02±1.04 to 0.84±0.84 (Danjoux et al., 1998). There is not enough detail or number of patients to compare with VISX. Flying-spot and other scanning lasers should also have greater versatility and good safety profiles, but peer-reviewed data are scant.

Environmental Effects

Few environmental effects of PRK and PARK have been studied (Butler, 1997 and Schallhorn, 1997a, 1997b). Mader et al. (1996) showed no change in effect with high altitude in comparison with RK. Subjective experience with hyperbaric conditions indicates no change. Any effect of UV radiation may be to induce regression or late scarring. There may be an effect on visual performance from low-humidity environments, especially during the first 3 months following surgery.

Potential harm to the surgeon and operating team from the laser plume and dispersal of particles has had limited study, implying very little scatter of viral particles toward the surgeon or technicians. Anecdotal reports of bronchitis in high-volume surgeons have not been peer reviewed.

LASIK versus PRK

At this time the paucity of published data on LASIK in comparison with PRK hampers any meaningful analysis. Key questions include:

1. Is there a difference in the achieved rate of 20/20 and 20/40 UCVA? Some reports indicate a lower rate of 20/20 although a higher rate for 20/40.
2. Is there a difference in stability? Surgeons suggest 20/20 at 1 day in a high rate of patients, but data suggest stability does not occur until 3 months which is similar to PRK.
3. What is the time to return to duty? What is the effect on productivity if service members can have bilateral surgery?
4. Is there a difference in loss of BSCVA? PRK now approaches zero with newer techniques. LASIK uses a mechanical keratome that has been associated with irregular astigmatism in previous uses (automated lamellar keratoplasty, keratomileusis) and early reports indicate 1–5 percent loss of two lines BSCVA.
5. What is the long-term rate of flap complications?
6. What are the late complications (incidence of flap dislocation, melting)?
7. What is the true rate of reoperations? Early reports were as high as 40 percent attributed to conservative treatments while developing the nomogram.
8. What is the effect on low frequency contrast sensitivity with LASIK that may require smaller ablation-zone diameters and has another potential optical interface in the mid-stroma?
9. What will be the environmental effects on LASIK? Hypobaric (high altitude), hyperosmolar (seawater), wind (shear), ocular trauma (not for burst, but for flap displacement), low humidity, cold (potential to shut down the endothelial pump and loosen the flap)?
10. What factors influence regression in LASIK? How do they differ from PRK?
11. Which patients should have LASIK as opposed to PRK and vice versa?
12. What is the optimum design for the microkeratome?

SUMMARY OF CONTROVERSIES AND GAPS IN KNOWLEDGE

Although PRK and LASIK are widely accepted and being performed worldwide, many controversies and gaps in knowledge exist with respect to safety, efficacy, and techniques.

PRK versus LASIK

There is much more information on the results of PRK, both in terms of immediate results as well as longer-term follow-up (1–5 years) than LASIK. This gap in knowledge makes discussion of the relative value versus the risks of LASIK incomplete and somewhat speculative. Because of the likelihood of permanent nonattachment of the central corneal flap in LASIK, there may be dangers of flap loss secondary to trauma. LASIK may be superior to PRK for myopia greater than -7.00 diopters, however, and may be associated with more rapid recovery and visual rehabilitation with reduced central scarring. High myopia (greater than
-7.00 diopters) may also be better treated with PRK using second-generation solid-state lasers not currently approved in the United States. Exposure to UV light may have less effects on a patient after LASIK versus PRK.

Most studies have been relatively short term with PRK and limited with LASIK. There is a significant gap in knowledge with respect to potential long-term complications of both of these procedures.

Multizone versus Multiple Pass

There is controversy in the size of the optimal ablation treatment zone in PRK. Best optical results appear to be achieved using a 6-mm zone or larger in PRK in comparison with the previously smaller zones. The ablation zone in LASIK is small by necessity. Spot size appears to be related to "islands" of residual tissue in the ablation zone with large spot size more likely to cause these islands. Multiple pass techniques allow for "drying" and reduce islands. Multizone techniques allow for wider, shallower ablation zones with "smoother" shoulders that may have many positive benefits including reduced haze, reduced halos, better low-frequency contrast acuity, and less regression.

Low Energy versus High Energy

There may be a benefit in using low-energy techniques versus high-energy techniques, especially in higher myopia (less haze, less regression of the treatment effect). Low energy corresponds to solid-state and small-spot-size techniques. These will have more versatility in patient selection (hyperopia and all degrees of astigmatism) and adjustability with potential for computer-controlled, individually designed ablations to create the optimal corneal shape for every patient.

Epithelial Removal

There are several methods available to remove the corneal epithelium prior to PRK: mechanical (FDA approved), laser transepithelial ablation, alcohol debridement.

Mechanical debridement of the epithelium with a brush is the most rapid technique but may be less complete than alcohol debridement. The significance of this is not well understood. Laser removal may stimulate less cytokine release from the unaffected edges leading to reduced apoptosis and scarring.

Epithelial Healing

There is little data to support the safety and efficacy of contact lenses in treating epithelial defects. Current practice includes contact lens wear to reduce pain, but is recognized to prolong the epithelial defect for approximately 1 day. In addition, ocular surface diseases such as rosacea, tear dysfunction, and obstructive meibomitis are known to retard healing and should be treated prior to PRK. Use of cytokines to retard apoptosis or to stimulate epithelial growth may prove beneficial.

Contact Lens Wear

Because PRK does not alter the peripheral corneal curvature (unlike RK which flattens it), patients can resume contact lens wear if required. There are no reported problems in the ability to wear contact lenses successfully after PRK, if needed.

Steroid Use After PRK

The use of topically applied corticosteroids following PRK is controversial because of potential complications such as steroid-induced glaucoma, cataracts, and herpes simplex infection. Currently, topical steroids are commonly used in the United States, but not by some European surgeons. More information is necessary to determine the optimum approach.

Spatial Contrast Sensitivity

The loss of low spatial contrast sensitivity following PRK during the first postoperative year is well described in the literature. There are no data that adequately address the issue of whether or not this is relevant to performance or is predictive of decreased visual function.

Performance Standards Pre- and Post Operative

It is critical to know how the performance of an individual is affected by PRK with respect to specific military duties. Pre- and postoperative tests need to be developed to assess the impact on specific areas such as night driving, pilot function, rifle performance, and SEAL performance.

4

PRK and Visual Function

Martin S. Banks,
Arthur Bradley,
James M. Brown

THE OPTICS OF PRK

Introduction

As an important prelude to an analysis of the experimental literature, we first develop a list of optical and visual issues important for PRK. This introduction provides a conceptual framework that will be used to organize and understand the lengthy and sometimes confusing list of experimental studies on PRK.

Efficacy

If PRK corrects the initial refractive error, then it is an *effective* procedure. A problem with **efficacy** results when the procedure leaves residual refractive errors. Of course, residual errors are likely, and the real **efficacy issue** becomes whether or not the residual refractive errors are "too large." Presumably, the criterion for too large will vary with individual and profession. The likely presence of residual refractive errors also raises the issue of whether an additional refractive correction will be used routinely or just for visually demanding tasks. For some individuals, a reduction from a 6 to 1.5 diopter of myopia will be considered effective and allow an individual to function adequately in many tasks (e.g., walking) without additional correction whereas, -6-diopter myopes are virtually "blind" without their glasses. Alternately, any residual refractive error in excess of -0.25 diopters would require additional refractive correction for some individuals such as pilots who must have 20/20 visual acuity.

One strategy to evaluate the efficacy of PRK would be to assess the percentage of those treated who are able to function without additional refractive correction. This assessment would likely show that the functional demands of specific groups of individuals will vary, and that **efficacy** will depend on who is being treated. From the military perspective, efficacy will certainly vary with military task.

Safety

There are several ways in which PRK can compromise vision and thus introduce a *safety* issue. Here we simply consider those examples that affect the optical quality of the eye and thus reduce visual capability. Metabolic, structural, and physiological safety issues are addressed in Chapters 2 and 3. We have divided the safety issues into three categories: over- and undercorrection, changing the shape of the cornea, and changing the transparency of the cornea. Several other issues are also addressed.

Overcorrection or Undercorrection

Overcorrection or undercorrection can be considered an efficacy issue, but may also compromise safety in the following ways:

1. Correction may not be stable. A stable residual correction can be corrected by routine use of glasses or contact lenses, but an unstable refractive status exhibiting diurnal or altitude-dependent variation [as did radial keratotomy (RK)] cannot be easily corrected. Also, the refractive changes initiated during the procedure itself may take months or years to stabilize.

2. Any over-correction (converting a myope to a hyperope) will move the patient's near point (the closest point that can be focused) farther away. For young adults, this is of little significance because their near points are so much closer than virtually all "near tasks" such as reading. However, for a patient in their 40's, this increase in the near point distance could compromise important near tasks because the near point is already farther away in this age group. A standard clinical solution to the increasing distance of the near point is to wear a "reading add" or bifocal, and this will be necessary at a younger age in those patients who have been "over-corrected". PRK can reduce the curvature of the cornea to cancel for myopia, but the final cornea may be too flat - inducing hyperopia. This is shown schematically in Figure 4-1.
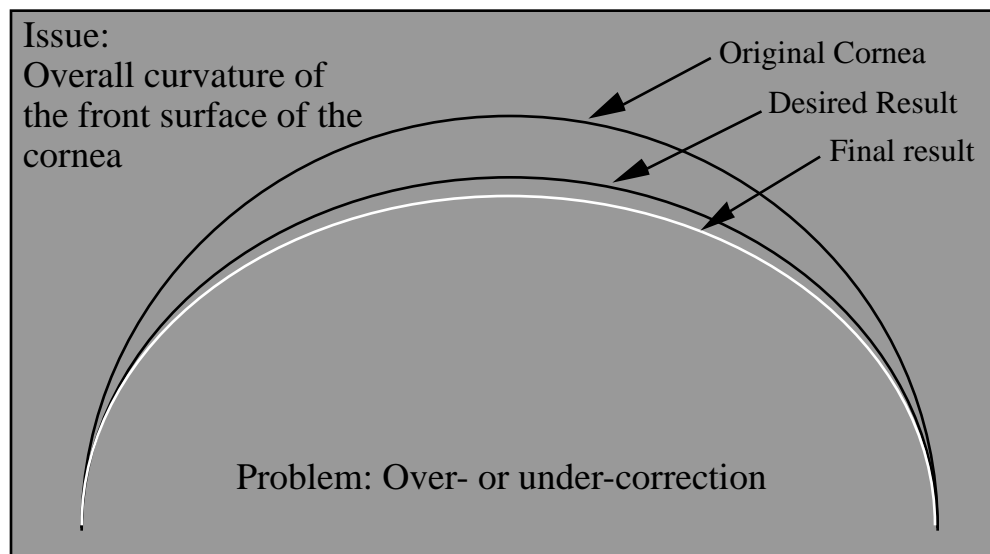

Issue:
Overall curvature of
the front surface of the
cornea

Original Cornea
Desired Result
Final result

Problem: Over- or under-correction

Figure 4-1. Overall curvature of the front surface of the cornea.

Experimental Data on Over- and Undercorrection

Finding 1.   Virtually all studies of refractive stability following the PRK procedure show a common pattern of post-PRK refractive error. The refractive error immediately following PRK is usually hyperopic (overcorrection), but during the first 2 or 3 months, the manifest refraction gradually becomes less hyperopic (more myopic) again. In some cases, this myopic regression results in emmetropia, but in others it leaves the patient hyperopic. In most studies, the final Rx after regression

has reverted to myopia (three such examples are shown in Figure 6 of Gartry (1991). In most studies, the refractive error stabilizes after about 3 months, but this finding is not universally observed and some studies report continuing regression in high myopes over a 1-year period.

The general pattern described above can be seen in the data of Kalski et al. (1996), Shah and Hersh (1996), Schallhorn et al. (1996), Ficker et al. (1993), Gartry et al. (1992a, 1991), O'Brart et al. (1994e, 1995). The most detailed data, broken down into groups identified by the magnitude of the preoperative level of myopia, show that the time taken to stabilize is longer for larger amounts of myopia. They also show that the myopic regression is much larger for higher myopia (e.g., about 1.5 diopters for a -2-diopter myope, and over 6 diopters for a 10 diopter myope). The later studies showed less and less myopic regression, and Schallhorn's recent data (his "refractive stability" graph shown to this panel in October 1997) have no identifiable regression. A plausible explanation for the range in regression data seems missing, as is an explanation for interstudy differences. One suggestion is that regression is an unavoidable consequence of the healing process that is simply delayed by the application of topical steroids. with the potential to re-emerge once steroid therapy is terminated.

Once post-PRK refractive error has stabilized, several studies have plotted the "final" Rx change against the desired Rx change. These scattergrams are reported by Shah and Hersh (1996), Schallhorn et al. (1996), Gartry et al. (1992a), O'Brart et al. (1994e), and two patterns are seen. In the Gartry data, the mean achieved correction is about 50 percent of the attempted correction (Gartry et al., 1992a, Figure 4), and the same pattern can be seen in the larger data set of Gartry, 1991 (but in table form). The later studies of Shah and Hersh and also Schallhorn show data in which the average achieved Rx is almost equal to the attempted Rx. This improvement in refractive results presumably reflects a change in the ablation algorithms or healing process. The final refractive error in Schallhorn et al. (1996) indicates that about 90 percent end up with an Rx within 1 diopter of emmetropia and 70 percent within 0.5 diopters. Schallhorn's 1997 data also report approximate emmetropia with most eyes.

Finding 2: From the literature, it appears that success rates are improving: Final post-PRK Rx's are getting closer (on average) to emmetropia. (See Table 3.1 for a comparison of three corporations' lasers.)

We are not sure why this change has occurred, but one can assume that implementation of some feedback will lead to further improvements in the accuracy (efficacy) of PRK.

Finding 3: Because ablation depth will vary with corneal hydration and healing processes, and because both can vary between eyes, it is unlikely that the standard deviations in achieved Rx will be able to be reduced to zero in the same way that the mean Rx can be refined.

The O'Brart et al. (1994e) study compared the accuracy of 4- and 5-mm ablation zones. They show data similar to Gartry's with the 4-mm ablation zone, but with data similar to Schallhorn's 5-mm ablation zone. Gartry (1991) used a 4 mm ablation zone, whereas Schallhorn used a 6-mm zone as did Shah and Hersh. Also, Kalski et al. (1996) compared 5- and 6-mm ablation-zone sizes and found less hyperopic overcorrection, less myopic regression, and smaller final refractive errors with the 6-mm ablation zone.

Finding 4: These results seem to indicate that large initial overcorrections, large myopic regressions, and large residual myopias can be avoided by using a larger ablation zone. We have not found any reasonable explanation for why larger ablation zones should produce improved refractive outcomes.

Finding 5: Stability of the post-PRK refraction has been studied under high-altitude conditions known to produce large hyperopic shifts in post-RK eyes. Unlike post-RK eyes, no hyperopic shifts were observed in the PRK eyes during a 3-day exposure to a hypobaric environment (Mader et al., 1996).

Data on Overcorrection or Undercorrection Missing from the Literature.

Means plus some measure of variability, such as the standard deviation or standard error of the mean, are very useful in identifying central trends in the data and providing an estimate of error. However, it is much more valuable to see data from individual eyes. For this reason, the scattergrams are important in that they can be used to identify the number of eyes that meet or fail to meet any number of criteria. Many reports fail to provide data on individual eyes. It is only reasonable to assume that the changes in refractive error are caused by changes in the anterior corneal curvature, but there are always other possible factors (e.g., corneal thickness, refractive index changes, etc.). However, many reports fail to include these data. This omission can be crucial. For example, pre-PRK myopic refractive errors are not likely to be underestimated, but post-PRK hyperopic errors are because the patient can mask such errors by accommodating. Also, the pupils of many patients in a dark clinic refraction lane may be larger than the ablation zone (when a 4- or 5-mm zone is used), so the refraction may not reflect the treated cornea only. The errors in refraction data are, therefore, potentially much larger than in keratometric data, and thus corneal curvature data are more desirable and easily restricted to the ablation zone. One study (Wilson, 1991) used a corneal topographer (as opposed to a standard keratometer) and reported central ablation power data. Plotting the achieved change as a function of the attempted change in a scattergram, they show a significant discrepancy between the two measures. Sher (1992) found only about 6 diopters of power change in the cornea while reporting about 10 diopters of change in the refractive error. Schallhorn (1997) showed keratometric data, but not for individual eyes and without any "target" with which to compare. The discrepancy between keratometric and refractive changes may be due to the keratometry testing "myopic islands" in the center of the ablations zone (see Figure 4-2).
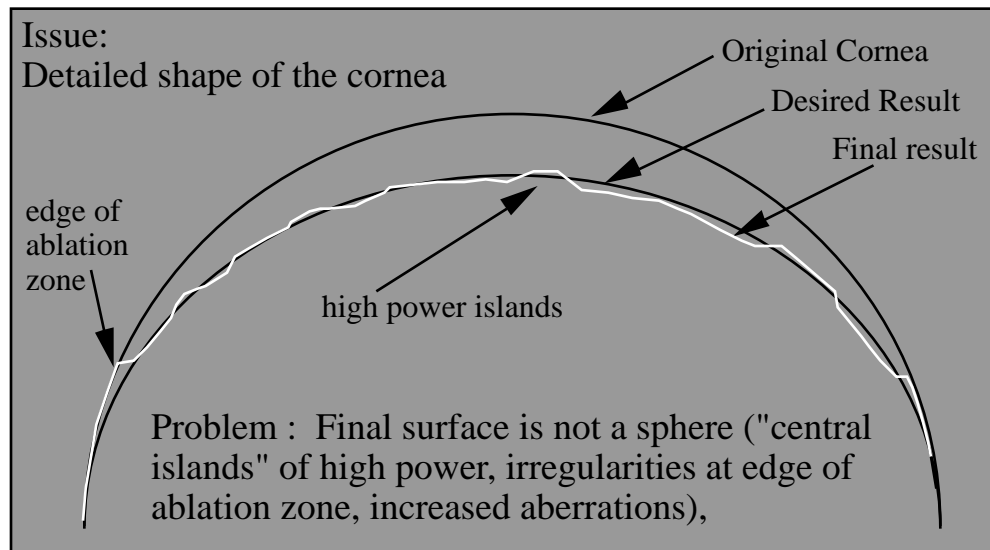
Figure 4-2. Schematic diagram showing a post-PRK cornea (in white) with the desired average shape necessary to correct the refractive error but with an irregular shape.

A new research paper (Smith et al., 1998) describes a methodology and the results in refractive surgery that may be a model technique to answer this question. The few other studies we can report seem to indicate that PRK does not produce the change in corneal power that it is designed to, but paradoxically, it does produce the desired change in refractive error. In addition to comparing corneal curvature changes with refractive changes, one study has reported the change in corneal thickness 1 month postoperatively and the authors observed the predicted 14-mm per diopter change in thickness indicating that the ablation depth and dioptric changes follow a simple model (Moller-Pedersen et al., 1997). It is worth noting that they did not achieve the desired ablation depth, indicating that the algorithms relating laser characteristics (intensity, duration, etc.) and ablation depth are not precise.

Because some of the earlier data were obtained with smaller ablation zones (e.g., 4 mm), and the refractions were probably obtained with larger pupils, we might expect there to be a myopic bias in these data because the refractions would be affected by the untreated cornea which is still myopic. This may explain the earlier myopic errors. Schallhorn et al. (1996) did not observe much difference in the uncyclopleged (manifest) and cyclopleged refractive errors, indicating that the untreated margins of the cornea had little impact on the cyclopleged refraction when a 6-mm ablation zone is used.

How accurate is the PRK procedure? Clearly, early procedures (e.g., Gartry, 1991, 1992a) were very inaccurate, but the most recent data (Schallhorn, 1996, 1997) seem to be very accurate. For example, mean residual Rx in Schallhorn's 1997 data is close to zero (-0.21). However, the standard deviation is still quite high (0.57 diopters). A scattergram or analysis showing the percentage who meet certain criteria would be valuable here (see Table 3.3).

Finding 6: Use of large (6-mm) ablation zones seems to correct two serious problems with earlier data collected with 4-mm ablation zones, and post-PRK refractions are stable and close to emmetropia.

Finding 7: Reliance on direct corneal measurement should be utilized to see if the procedure actually changes the cornea by the desired amount because post-PRK Rx is an indirect measure that can be influenced by pupil size.

The DoD should consider research to resolve inconsistencies in the literature. To be convinced that PRK actually does what it is supposed to do requires a single study to monitor (1) Rx, (2) corneal thickness changes, and (3) corneal curvature changes. Using a simple model, these data can confirm the success or failure of PRK. We can find no study that has formally tested the refractive effects of PRK in this way.

Changing the Shape of the Cornea

Any well-designed optical system will focus virtually all light rays from a point source into a point image. However, even the best optical systems are imperfect, and rays passing through different parts of the pupil end up in slightly different locations in the image plane. This happens because there is only one possible shape of an optical surface that will create the "perfect image," and this shape is not a sphere. All shape deviations from this ideal will lead to an "aberrated" image and reduced image quality. Because the presurgery eye is not aberration-free, it is possible that PRK could either increase the optical aberrations of the eye or decrease them. Current systems have no built-in strategies to modify the eye's aberrations because they (we think) operate on simple spherical or paraxial assumptions about refraction and image quality.

The presurgery eye will have significant positive spherical aberration and coma created by surface deviations on the order of a few micrometer from the ideal. To avoid introducing further aberrations, PRK must have micrometer level accuracy. There are

two obvious ways in which PRK can, and probably does, introduce additional aberrations into the optics of the human eye.
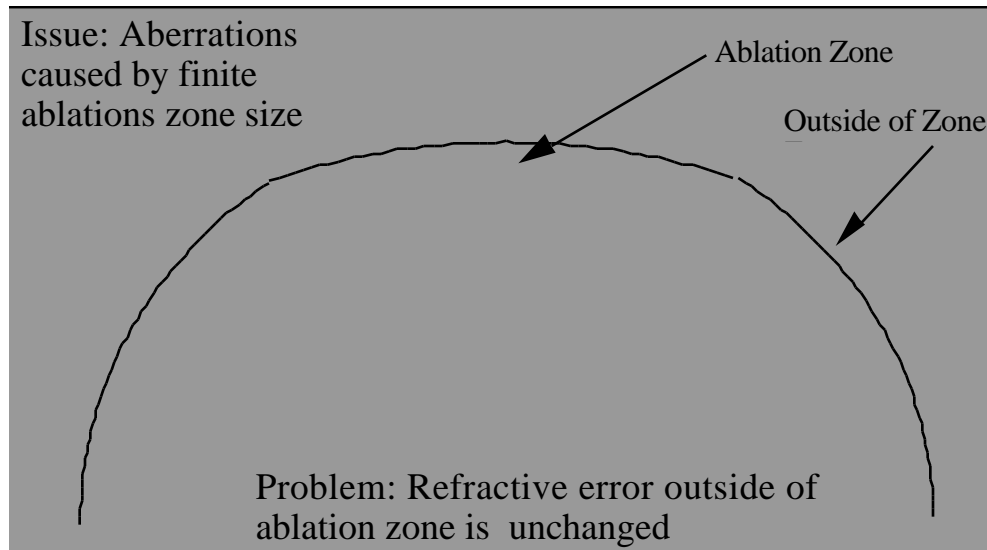
1. Whenever the ablation process is not uniform, the obtained ablation depth will deviate from that prescribed, and changes in ablation depth will introduce irregularities in surface power, sometimes referred to as "high-power islands."

2. Because the ablation zone does not cover the entire cornea, PRK must introduce an optical irregularity at the edge of the ablation zone. One simple way to think of this is that the post-PRK cornea will have a lower power within the ablation zone than outside of the zone, effectively creating a "bifocal" cornea. Alternatively, PRK can be considered to change the eye's spherical aberration. Virtually all eyes exhibit some positive spherical aberration (more myopic at the edge than at the center of the optics), and PRK will further exaggerate the power difference between the center and periphery of the optics thus increasing the eye's positive spherical-like aberration (as shown for RK). Of course, this aberration is really nothing like true spherical aberration because it originates from an asphericity of the cornea (the edge of the ablation zone). This type of dioptric discontinuity has been modeled by Charman (Charman and Walsh, 1986; Charman and Saunders, 1990) for bifocal contact lenses, and when the marginal optics are defocused, the defocus produces an annular blur pattern. The size of this blur annulus depends on the magnitude of the defocus and the diameter of the refractive annulus which in turn will be determined in PRK by the size of the ablation zone and the size of the pupil. This blur annulus could be characterized as a halo by a patient.

Experimental Data on Changing the Shape of the Cornea.

The following analysis looks at halos caused by aberrations, but halos can also be caused by changes in epithelial transparency (see next section).

Aberrations introduced by PRK will be caused by changes of the surface curvature. The pretreatment cornea is not aberration-free, and therefore, it is possible that the PRK could either increase or decrease aberrations. Currently, the concern is that PRK (like RK) increases corneal aberrations. The consequences of increased aberrations are twofold. First, the visual capabilities of normal eyes with large pupils (e.g., >3 mm) are optically limited by the aberrations that reduce acuity *and more significantly reduce sensitivity to contrast in larger objects*. Second, the clinician's view of the fundus is limited because of the highly aberrated dilated eye that renders most low-contrast details in the fundus invisible (e.g., all but the very large blood vessels). (The invisibility of the low-contrast vasculature in fundus photography and ophthalmoscopy should be evidence to all ophthalmologists that the reduced image contrast caused by aberrations is important for the visibility of spatial details that are much larger than the "resolution limit." In general, a test of contrast sensitivity would pick up this contrast attenuation psychophysically.) In a normal, healthy pretreatment eye, the detrimental effects of aberrations will generally increase with pupil size. The specific concern about PRK is that increasing pupil size will lead to a larger than normal increase in aberrations. This hypothesis is based on the simple model of the post-PRK cornea: the post-PRK cornea is exactly as specified by the algorithm (see Figure 4-3) with a decreased radius centrally, but unchanged radius peripherally.

Issue: Aberrations caused by finite ablations zone size

Ablation Zone

Outside of Zone

Problem: Refractive error outside of ablation zone is unchanged

Figure 4-3. Aberrations caused by finite ablation-zone size. PRK produces a bi-focal cornea with a low power central zone and a higher power annual zone.

Fortunately, this type of optics has been studied quite extensively within the contact lens field because numerous designs of bifocal contact lenses employed such a "center-surround" optical design with different optical power in the center zone (bifocal intraocular lenses have also been used). The image quality of such bifocal systems are inherently lower than monofocal systems, and the image will consist of a focused image from the center and a defocused annulus from the surround. Thus, when looking at a bright point source, it will appear to have an annular halo. When the central optics is focused, the size of the halo is determined by the dioptric difference between the center and surround and the size of the annulus such that the halo diameter (radians) will be approximately equal to the product of the dioptric difference (defocus in diopters) and annulus diameter (meters). The inner diameter of the halo will be determined by the size of the ablation zone whereas the outer diameter will be determined by pupil size. The amount of light in the annulus will be determined by the difference in ablation-zone size and pupil size. Based on this simple model, we might expect larger pupils to produce larger outer diameters for the halo, and also larger mean diameters. We might also expect more light in the annulus when the ablation zone is smaller, but a smaller inner-diameter and a smaller mean diameter halo for the smaller ablation zone. Halos will be invisible when the pupil is smaller than the ablation zone.

Several reports have observed and measured these types of halos in post-PRK eyes, but none have quantitatively applied the simple model above to the problem, and the results are a bit confusing.

Finding 8: Post-PRK eyes do experience halos when the pupil dilates at low light levels [(78 percent in the early postoperative period according to Gartry (1992)]. As predicted, halo size is correlated with pupil size and with induced refractive change, and they are larger when an overcorrection is produced and they decline with the myopic regression. Because these annular blur circles are caused by defocus of the light passing through the pupil margins, they can be reduced in size and eliminated by correcting this defocus. Of course, correcting the defocus outside of the ablation zone will introduce defocus within the ablation zone, and thus the blur annulus will be replaced by a blur circle. When these experiments are done, patients do report

that correcting the peripheral optics reduces the halo size (O'Brart et al., 1994). The data of Gartry et al. (1991) provide a good quantitative fit to the above model in that if you ignore those who did not see halos (pupil too small?), the lens power necessary to eliminate the halo is close to the difference in refraction between the center and periphery of the cornea. One study identified people who suffered from night driving problems post-PRK (see discussion on night vision below), and gave them a mild miotic (Dapiprazole) to see if this solved the problems. They created between 0.75- and 3-mm reductions in pupil diameter, and most patients experienced significant improvements (Alster et al., 1996).

Finding 9: The dioptric step introduced into the peripheral optics makes the eye more myopic at the pupil margin (outside of ablation zone) than at the pupil center (within the ablation zone). This bifocal nature of the post-PRK cornea should also be present in a post-LASIK cornea. In normal eyes, this trend is often referred to as "spherical aberration" and more accurately as "spherical-like" aberration because the cornea is not truly spherical. Of course, after PRK, the dioptric step at the edge of the ablation zone is far from spherical, but some investigators refer to the increased aberrations in PRK as increased spherical (Seiler et al., 1993) or spherical-like aberration (Martinez et al., 1998) because the normal trend seen in spheres and normal eyes is exaggerated in post-PRK eyes.

The aberrated nature of the cornea can be readily observed using standard corneal topography instrumentation, and the edge of the ablation zone does show up with this technology as a power step (Hersh et al., 1996; Martinez et al., 1998; Seiler et al., 1993).   One study used the corneal topographic data to compute standard Seidel aberrations (which may not be appropriate for a post-PRK cornea) for different pupil sizes. Interestingly, the authors observed a reduction in the aberrations for 3 mm pupils after PRK. Quantifying the relative increase in spherical-like aberrations, Martinez et al. (1998) show that the normal 7-fold increase that occurs when increasing a 3-mm to a 7-mm pupil in normal eyes increases to a 300-fold increase in post-PRK.

A seemingly unrelated aberration-like problem was reported by Maguen et al. (1994) and Kalski et al. (1996). They reported seeing central corneal areas exhibiting more myopia than the surrounding areas within the ablation zone. Maguen et al. report this in 5 percent of their eyes with a size ranging from 1 to 3 mm in diameter with a refraction of 3-diopters more myopic than the surrounding ablation zone present from 3 to 6 months postoperatively. However, they may have underestimated the frequency of these transient islands because they were not looking for them in every eye. A more recent study (McGhee et al., 1996) found that 29 of 100 eyes had a topographic myopic island of more than 3 diopters within the ablated zone at 1-month postoperatively; all but 3 had resolved by 6 months. The incidence of myopic islands was higher with higher levels of initial myopia. Presumably, a much larger percentage would have exhibited myopic islands if a criterion of less than 3 diopters had been used.

It is thought that these islands are caused by regional differences in corneal hydration during ablation, nonuniformity of the excimer beam, or absorption of the laser beam by the plume of ablative products, or regional differences in healing. No definitive cause has been identified. Recent ablation algorithms used by the VISX laser add extra ablation to the center of the zone to eliminate the possible myopic islands. Also, they do not seem to be produced by the Autonomous laser.

Finding 10: Topographical studies report myopic islands in the center of the ablation zone, which may be absent with newer lasers.   It is not clear what produced them or why they generally disappeared after 3 months.

Martinez et al. (1997) observed large amounts of vertically oriented coma-like aberrations, and they suggest that this may reflect a structural weakening and subsequent "sagging" of the cornea under the influence of gravity.

One study (Lohmann et al., 1993) measured halo size (not intensity) on a range of myopes using a variety of different refractive strategies (glasses, hard contact lenses,

soft contact lenses, and PRK). They found that PRK produced halos similar in size to those seen by myopes with soft lenses and soft contact lenses, and all these were much smaller than those seen by myopes with hard contact lenses.   They concluded that "halos are not a problem for patients after PRK" because the halos are of similar size to or smaller than those seen by other myopes. This study needs repeating given the numerous reports of halos being the primary cause of patient dissatisfaction with PRK. It is important to emphasize that the visual impact of a halo will be determined by its intensity as well as its size, and the O'Brart data on size provide inadequate information to evaluate the relative impact of PRK halos over those experienced with other forms of myopic correction. Lohmann et al., therefore, overstep their data when concluding that the halos in PRK are not a problem because they have a similar or smaller size to those reported by non-PRK myopes.
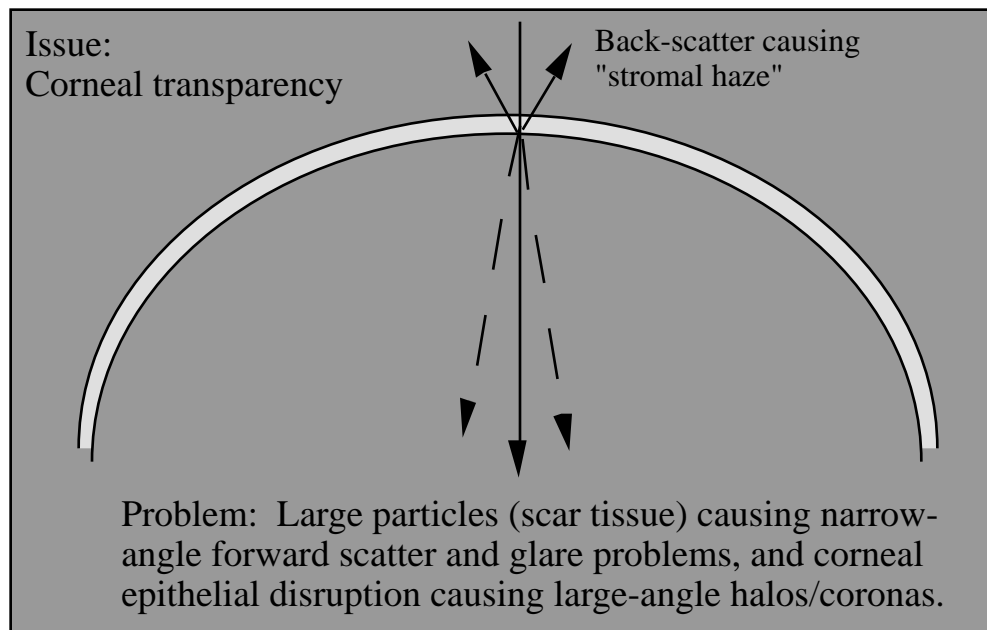

Changing the Transparency of the Cornea

When light interacts with matter it can be absorbed as in opaque material, it can be transmitted as in transparent material, and it can be scattered as in frosted glass and thin clouds. In optical instruments, optical materials are specifically chosen for their transparency properties, which can be either high or low (e.g., some clinical retinal imaging systems have high transparency for visible light, but low transparency for potentially hazardous but clinically useless UV and infrared radiation).   The eye's optical system has a similar transparency profile: high in the visible range and low (very low) in the UV and low in the infrared range. Indeed, the low transparency in the UV is caused by high corneal absorption in the UV that is the very basis of the UV photoablation technology used in PRK. Most optical systems strive to minimize scatter.
The potential impact of PRK on corneal transparency can only be understood by first clarifying the basis for corneal transparency. The corneal stroma is not an optically uniform material, but made up of a regular array of very small (19–34-nm-thick) collagen fibrils. Each one will scatter some light. However, because the size of these individual scattering sources is smaller than the wavelength of light (e.g., 400–700 nm), there is no constructive interference from these millions of scattering sources, and thus, effectively zero-scattered light reaches the retina and the cornea appears highly transparent in the visible range.   Corneal epithelium cells have a higher refractive index than the intracellular space, and this differential refractive index can also lead to diffraction effects at the cell boundaries. This potential diffraction/scatter effect in the epithelium is virtually eliminated by the tight junctions between corneal epithelium cells. However, under osmotic and physiological stress, fluid builds up between corneal epithelial cells and diffraction halos are seen.
There are two potential sources of reduced transparency and increased scatter following PRK:
1. Scar tissue and the formation of other small opacities and irregularly shaped collagen fibrils following PRK introduce scattering sources (see Figure 4-4). (See also Chapter 2, on wound healing.) These scattering sources can produce a backscatter that will be seen by the clinician as "haze" and forward scatter that will affect retinal image quality and will be seen as "glare" by the patient (see also discussion in Chapter 2). Different scattering sources produce different amounts of backward and forward scatter, and the angular distribution of the forward scatter also varies with the optical characteristics of the scattering source.   In general, most scattering sources have an angular dependence distributing more light at narrow angles than at large angles. This means that more of the scattered light will fall near to a light's retinal image than far from it. Alternatively, this means that bright lights near to a target will create a bigger glare problem than bright lights far from a target.

Figure 4-4. Corneal transparency.

      2.   Transparency of the corneal epithelium depends on the absence of intracellular spaces. If water accumulates in the intracellular space, diffraction will occur. The amount of diffraction is determined by the difference in refractive index between intra- and intercellular material and the size of the spaces. Because corneal epithelial cells are similar in size across the cornea, the intracellular spaces create a kind of diffraction grating at all orientations, and thus a circular diffraction patter occurs in the eye, which is seen as a halo by the patients. This is a common problem encountered by those with corneal edema because the corneal epithelium absorbs water, which it will do when it is physiologically compromised (often seen in patients who sleep with their contact lenses in, which deprives the cornea of oxygen). Because the physiological state of the cornea is maintained primarily by the corneal endothelium and epithelium, visible halos might indicate that the PRK procedure has compromised the physiology of these tissues.

Experimental Data on Changing the Transparency of the Cornea

      Following reports of clinical haze (back-scattered light) in the ablated zone, numerous studies have looked into the transparency and light scattering of the post PRK cornea. Clinically, haze is scored on a 0–4 scale, and increased haze post-PRK has been reported in many studies (see summary in Gartry et al., 1992b). The time course for haze development seems to peak between 1 and 3 months postoperatively (Kalski et al., 1996; O'Brart 1994E, Lohmann, et al., 1991a), and in many eyes the haze never returns to preoperative levels. Limited data seem to show that smaller ablation zones are associated with more haze (4 mm compared with 5 mm in O'Brart et al., (1994); and 5- and 6-mm zones compared in Kalski et al.)].

      Several methods have been developed to objectively quantify this haze. Lohmann et al. divide the light reflecting off of the post-PRK cornea into "reflected" and "scattered" light. Both seem to increase. From their methods, it appears that these two

categories refer to specularly and diffusely reflected light. Clinically, haze would correspond to diffusely reflected light. A recent and elegant study by Moller-Pedersen et al. (1997) was able to localize the source of this backscatter as the subepithelial region of the cornea (nerve plexus, Bowman's membrane) using confocal microscopes scanned through the cornea. They observed a clear correlation between the objective measure of backscatter and clinical haze grading. A different objective system (Maldonado, 1996) also found a good correlation with the subjective measure of haze, and they also report convincing data showing that the haze decreased steadily over the first year postoperative.

A recent study by Corbett et al. (1996) has identified three underlying causes of the corneal haze and the visual glare it produces (backward and forward scatter, respectively): epithelial surface disruptions (peaks at 1 week), subepithelial keratocyte disturbance caused a longer lived optical scattering (first month postoperative), and then a longer-lasting effect produced by deposits at the subepithelial/stromal boundary that lasted several months.   In some patients these glare sources do not resolve completely. A histological study by Lohmann et al. (1991) showed that the corneal epithelium had completely covered the ablation zone after 2 weeks. Although the central thickness of this new epithelium was normal, they found epithelial thickening around the edge of the ablation zone. They found irregularities in the Bowman's layer/corneal stroma boundary that were most pronounced at the edge of the ablation zone. Also, small vacuoles were observed in the most anterior stromal layers. They observed only a small number of keratocytes in the basal epithelial layer, which also increased in number toward the edge of the ablation zone.

Perhaps the most interesting aspect of the data presented by Lohmann et al. is that the potential scatter sources are more pronounced at the edge of the ablation zone. Although there is no explanation given for this, the visual consequences are clear: Scatter will be greater with smaller ablation zones or larger pupils (whenever the edge of the ablation zone is within the pupil). Most scattering sources produce both forward and backward scatter. The clinician sees the backscatter, but it is the forward scatter that interferes with vision and is typically referred to as disability glare. Several approaches have been used to study the forward scatter but they all involve measuring its effect visually. Forward scatter should reduce contrast sensitivity, reduce low-contrast visual acuity, and produce larger reductions in vision in the presence of a glare source.

Summary:

Finding 11: Clearly, the ablation process causes the usually very transparent corneal stroma and corneal epithelium to lose some of its transparency. This transparency loss peaks during the first month(s) and declines possibly back to normal levels at 3+ months. The method for removing the epithelium prior to the stromal ablation may also influence the amount of transparency loss. The biological causes are not clearly identified and need to be before a rational approach to eliminating them can be initiated. The backscatter produced will reduce the visibility of the fundus and potentially reduce the efficacy of a clinician to detect retinal pathology (but we could find no mention of this in the literature). Of more significance will be the forward scatter and the resulting loss of vision. The effect of all forward scatter will be most pronounced for low-contrast targets and low-intensity targets with adjacent high-intensity sources as often occurs at night. Interestingly, there is some evidence that the glare sources are more pronounced around the edge of the ablation zone, and this would further exaggerate the nocturnal effects because pupil size will increase at night.

The glare effects peak early in the postoperative period (2–3 months, and are virtually absent at 1 year in most eyes). However, there are persistent glare and haze

problems that linger in some eyes. Currently there is no clear hypothesis to explain why some eyes have persistent haze. **There are significant gaps in our knowledge about the optics of these transparency losses. How much light is scattered and what is the angular distribution of the scattered light?**

Other Optical Properties of PRK

Magnification

Any time that a negative spectacle lens is used, it will optically minify the retinal image. However, because retinal images in myopic eyes are larger than those in emmetropic eyes, it turns out that the spectacle minification reduces the previously magnified (but defocused) uncorrected myopic image to the size of an emmetropic image. If the spectacle lens is replaced by a correction in the corneal plane (contact lens or PRK or RK) then the original uncorrected magnification is retained. That is, myopes corrected at the corneal plane have larger retinal images that emmetropes. This means that if all other image quality parameters remain constant, switching a myope from a spectacle correction to a PRK or contact lens correction will lead to an increase in visual acuity (Applegate and Howland, 1993; Applegate and Chundra, 1995; Strang, et al., 1997), but the effect is small (about 0.1 log MAR per 17 diopters of myopia).

Optical Centration

Optical quality in any multiple element system depends critically on the alignment of the individual components (lenses and apertures). In the human eye, this general issue is complicated because, in addition to an optical axis, the human eye has its own neural axis anchored at the fovea.   Optimal foveal image quality can be expected when the optical axis and neural axis align. Of critical importance is the alignment of the pupil and cornea. For foveal image quality to be optimized, the corneal center of rotation should be aligned with the primary line of sight (line connecting the fixation target to the center of the entrance pupil).   When this condition is met, the optical beam passing through the pupil will have been imaged symmetrically by the cornea, thus avoiding comatic aberrations. Typically this is not the case in normal eyes, and the pupillary axis and primary line sight differ by varying amounts; the angle that separates them (angle) is often quoted as being 5 degrees, but it varies from one individual to another.

We have found no systematic explicit study of angle   in the PRK literature. Most studies of centration do a poor job of articulating what is being measured, although we think most measured the right parameters.   Instead of describing the alignment in angular terms, they describe misalignment in millimeters (in the plane of the entrance pupil). Examining this misalignment is a standard part of any optometric exam (e.g., the Hirschberg test). One study correctly suggests that the PRK procedure (and thus, we suspect, the post-PRK cornea) be aligned with the primary line of sight (Uozato and Guyton, 1987). This can be achieved by having the treatment and fixation beams coaxial, and from the perspective of the clinician (also coaxial) the treatment beam is centered in the entrance pupil. We believe that this is done (e.g., Cavanaugh, 1993b). Evaluating the centration of the ablation zone also needs to be referenced to the primary line of sight, and earlier studies in which centration is compared, the "corneal vertex" are fairly useless (e.g., Cavanaugh, 1993b). Most studies have evaluated the centration relative to the pupil using corneal topography instruments that locate the entrance pupil. Because, these instruments may have the patient fixate a point coaxial

with the annular rings, and the image is captured by a coaxial optical system, effectively they are measuring angle .

It is important to appreciate that correctly aligning the final post-PRK cornea requires alignment within the laser, alignment by the clinician, and fixation by the patient. Errors in any of these will result in a misaligned cornea. Because the pre-PRK cornea is not typically aligned with the primary line of sight, the post-PRK cornea can in principle have less coma and thus produce better image quality.

Most studies show that alignment is within 1 mm for almost all eyes, with average errors of 0.4 mm (Cavanaugh, 1993a), 0.36 mm (Lin, 1993), 0.88 mm (Klyce and Smoleck, 1993), and 0.4 mm (Doane et al., 1995) are reported. Two important questions need to be addressed; (1) What is the visual effect of decentration? (2) If decentrations tend to be biased in one direction or another, can the procedure be modified to correct for this?

Klyce and Smoleck (1993) found that best-corrected high-contrast visual acuity was unaffected by ablation-zone decentration. A similar result was observed by Cavanaugh (1993b). Verdon et al. (1996) found that low-contrast visual acuity did decline with increasing decentration, and Klyce and Smoleck (1993) showed that halos and night driving became worse with increasing decentration.

There appears to be a systematic error in the procedure (or the alignment evaluation) in that some studies report an absence of perfectly aligned corneas (i.e., the distribution of errors has a gap at zero).

Finding 12: The level of optical data on PRK is clearly inadequate. In most cases the optical changes are inferred from indirect measures of visual function or from techniques developed primarily to quantify the optics of normal eyes that may be inappropriate to measure PRK eyes. Better optical methods are available and should be employed.

VISUAL PERFORMANCE MEASURES AND PRK

The preceding optical analysis points to two lingering optical problems that cannot be corrected by standard refractive techniques (soft lens or contact lens) : forward scatter from wound and healing in the subepithelial layers of the corneal stroma and the large dioptric "step" at the edge of the ablation zone. Both optical changes are likely to produce their major effects on retinal image quality during nighttime conditions. It is clear, therefore, that tests of visual function at night are the most likely to uncover any post-PRK vision problems, and these effects are to be exaggerated with difficult to see (low-contrast) targets. However, most tests of post-PRK vision have been performed at photopic light levels with high-contrast targets. There is a genuine need for vision tests to be administered under more typical nocturnal conditions.

There is a second problem specific to the military. Most military operations need to be executable at night and in poor visibility conditions (e.g., smoke screens), and therefore low light level and low-contrast tests of vision might seem ideal for evaluating the impact of PRK on the military mission. Unfortunately, there is no simple rule that connects visibility of low light level low-contrast targets to the ability to fly an aircraft or shoot a rifle, etc. Therefore, it may be necessary for the military to evaluate the impact of PRK on some real world nocturnal tasks.

Theoretical Considerations

Before examining the literature on visual consequences of PRK, it is extremely important to examine the theoretically predicted effects of the potential optical problems described in the first section of this chapter. The potential problems caused by (or corrected by) PRK are optical, so we need only assess the visual consequences of the set of optical effects that can occur. The most significant problem in making such a determination is how to relate a given optical degradation to the ability to perform a particular task in the military setting. For example, some subjects may suffer a small optical degradation due to PRK, but it is impossible at this point of our understanding to predict what performance degradation would occur in a particular situation such as using night vision goggles to fly at low elevation at night. Therefore, we divide our discussion into two parts. In the first, we will discuss how one can determine what the simple visual consequences of PRK are. In particular, what is the expected visual acuity, contrast sensitivity, sensitivity to glare sources, etc. In the second part, we make some recommendations concerning future research that will be required to determine performance in the military setting.

There are two potential approaches to determine the simple visual consequences of PRK: (1) direct measurement of optical effects (e.g., evaluate corneal power, corneal shape, forward scatter, and residual refractive error) and (2) indirect measurement of optical effects by using psychophysical tests from which the optical effects can be determined. The first approach has the advantage of being direct and, therefore, involves fewer assumptions. The second approach, however, has the significant advantage of being much easier to implement so that it can be used in a wide variety of settings. We develop the theory behind the second approach below because we believe it can provide quite accurate measures of optical degradation when applied properly and because it is so much easier to implement. We first consider, however, some means of direct optical measurement.

Direct Optical Measurements

A standard keratometer can provide a good estimate of corneal curvature. Numerous instruments can be used to measure the shape of the cornea. Most commonly used are "corneal topographers" that measure the size of the reflected image from the cornea and by simple equations convert reflective power to refractive power. Backscatter from the cornea can be measured using a photocell or other physical devices, and one clinically available instrument exists, but its accuracy has been questioned. Corneal haze is often assessed by the clinician using a 5-point scale, but some studies have used instruments that measure the intensity of the backscattered light that creates the haze seen by clinicians.

Psychophysical Measurements

Because PRK affects the optics and not the retina and central visual pathways, measures of visual performance need only assess how optical degradations affect the patient's ability to see. This makes the analysis of visual performance much easier than if the other parts of the visual process were involved. It is easier because the optics of the human eye are linear, and therefore the transmission of an arbitrary pattern of light onto the retinal image can be calculated to a very high degree of accuracy by use of linear systems analysis. This can be accomplished in two ways which are represented below by Equations (4-1) and (4-2):

$$\mathbf{i(x,y)} = \mathbf{o(x,y)} \otimes \mathbf{h(x,y)}, \qquad\qquad\qquad (4\text{-}1)$$

$$\mathbf{I(\ ,\ )} = [\mathbf{O(\ ,\ )}][\mathbf{H(\ ,\ )}]. \qquad\qquad\qquad (4\text{-}2)$$

In Equation (4-1), the spatial distribution of light in the object is represented by $\mathbf{o(x,y)}$ and the distribution of light in the retinal image is represented by $\mathbf{i(x,y)}$. The response of the optical system of the eye under consideration is represented by $\mathbf{h(x,y)}$, which is called the optical point-spread function. Equation (4-1) shows that retinal image distribution (*i*) can be calculated by convolving the object distribution (*o*) by the point-spread function (*h*). Thus, we can calculate the retinal image distribution for any object if we know the point-spread function of the eye under consideration.

Equation (4-2) represents the same process, but in terms of spatial frequencies rather than in terms of spatial distribution. $\mathbf{I(\ ,\ )}$ and $\mathbf{O(\ ,\ )}$ are the Fourier transforms of $\mathbf{i(x,y)}$ and $\mathbf{o(x,y)}$, respectively; they represent the spatial frequencies within the retinal image and object, respectively. $\mathbf{H(\ ,\ )}$ is the Fourier transform of the point-spread function (*h*); it is called the optical transfer function or OTF. The OTF describes the attenuation (and phase shift) that information at different spatial frequencies undergoes in passing through the optical system. An OTF of a normal human eye with its refractive error corrected is a low-pass function whose shape depends on refractive error, optical aberrations, pupil size, and retinal eccentricity. For the problem under consideration in this volume, we consider imaging onto the fovea only, so we do not need to consider variations in retinal eccentricity. At a pupil diameter of 3.0 mm and a spatial frequency of 20 cycles/degree (cpd), the OTF has a value of ~0.5 and this means that an object contrast of *m* will yield a retinal image contrast of $\sim m(0.5)$. The OTF is a complete description of the transmission of information from the outside world into the retinal image (at the fovea) for the viewing situation under consideration. In other words, if we know the OTF of a patient in a particular viewing situation, we can calculate the retinal image. We can learn a lot then about the visual consequences of PRK by measuring the OTF. Before describing how this might be accomplished, we consider the factors that are known to affect the OTF of the normal eye.

Figure 4-5 shows schematically a series of Modulation transfer functions for a normal eye that has been subjected to different types of optical degradation. The degradations include refractive error, spherical aberration, and forward scatter (glare).

An increase in blur causes a decrease in the transmission of high-spatial-frequency information; there is little effect at low spatial frequencies. The reduction of high-frequency transmission due to refractive error is very dependent on pupil diameter. In particular, the reduction is less significant when pupil size is small because of the increased depth of focus commensurate with small apertures.

The effect of spherical aberration is also shown in Figure 4-5. Interestingly, the decrease in optical transfer is largest at the medium rather than the high spatial frequencies. The magnitude of the degradation due to this aberration will depend on pupil diameter.

The effect of forward scatter is also shown in Figure 4-5. The decrease in optical transfer is now more similar across a wide range of spatial frequencies.
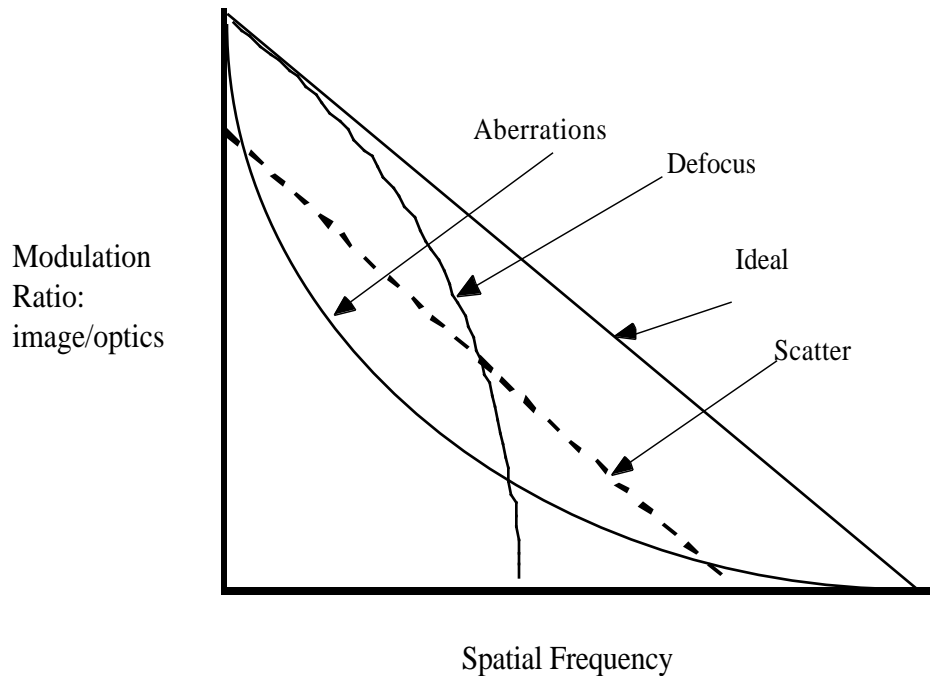
Figure 4-5. Schematic diagram showing Modulation Transfer Functions (MTFs) from four different optical systems. The optical effects of defocus, aberrations, and scatter are compared.

       Figure 4-5 makes clear that different causes of optical degradation produce different types of information loss at the retina. If a test were designed such that it was sensitive only to information at high spatial frequencies, fairly large amounts of spherical aberration might have little effect, whereas small amounts of refractive error would have a large effect.

       For the problem under consideration in this volume, we can make the assumption that PRK surgery affects only the optics and not the retina or central visual pathways of the patient. Thus, we can assume that changes in visual performance after surgery are due to changes in the patient's optics only. For this reason, if we have the right test, a comparison of visual performance before and after surgery will reveal the optical consequences of the procedure. Measurement of contrast sensitivity is an ideal candidate. In contrast sensitivity tests, the contrast of a sinusoidal grating (at a particular spatial frequency and luminance) is increased from a low value until it reaches threshold. A plot of the reciprocal of contrast at threshold as a function of spatial frequency constitutes the contrast sensitivity function (CSF). The foveal CSF for a normal observer with good vision under typical indoor lighting conditions is shown in Figure 4-6. The function is bandpass with peak sensitivity at 3–5 cpd. At progressively higher spatial frequencies, sensitivity falls monotonically to the so-called high-frequency cutoff at about 50 cpd; this is the finest grating an observer can detect when the contrast is at its maximum of 100 percent.
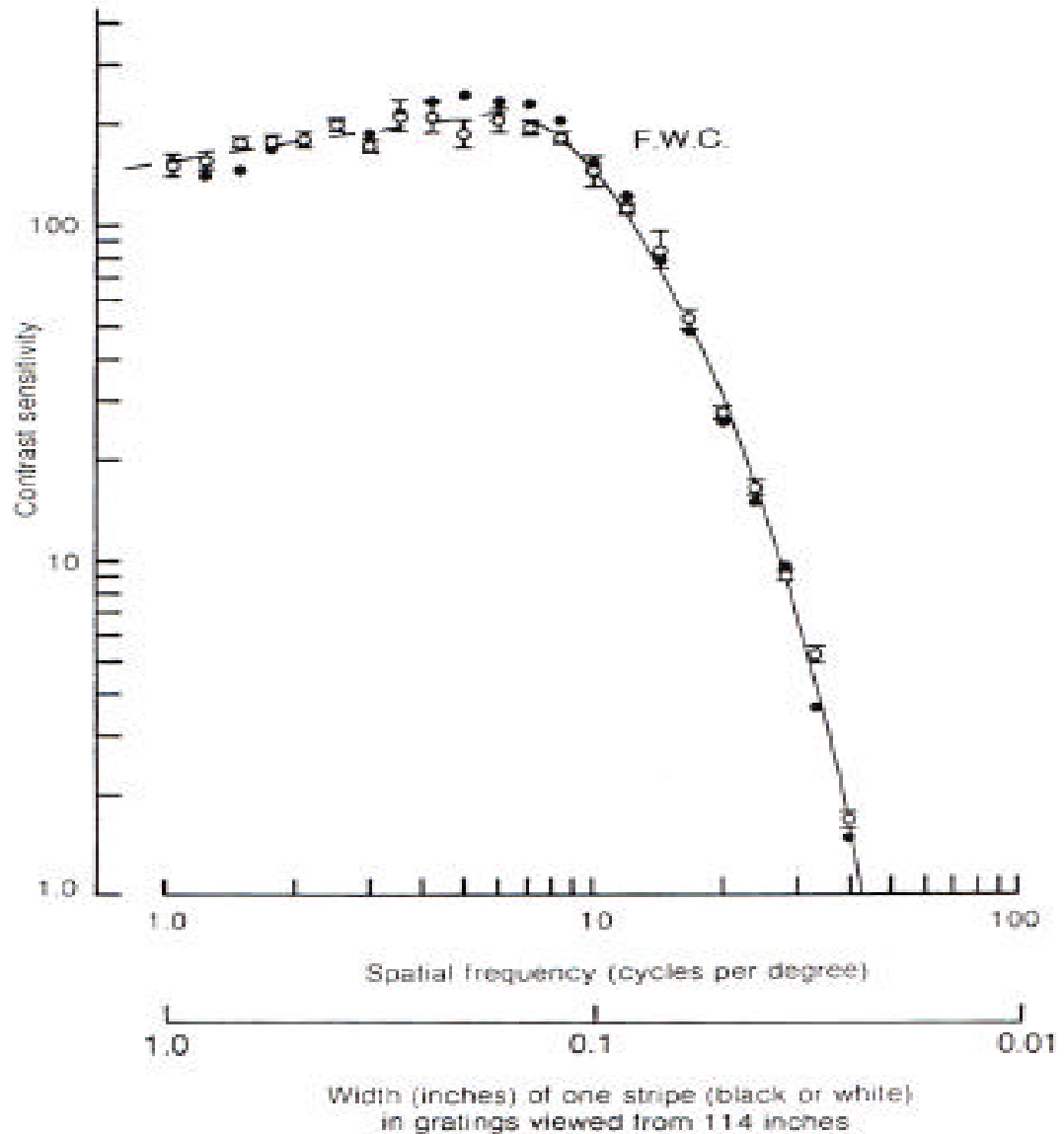
Figure 4-6. The foveal Contrast Sensitivity Function (CSF) for a normal observer.

Let C(w) represent the CSF of an observer. (Only the spatial frequency w is represented because here we consider a one-dimensional analysis for simplicity.) One can assume, with good justification for the problems considered in this volume, that

$$C(w) = [O(w)] [N(w)],$$

where O(w) is again the eye's OTF and N(w) is the transfer function associated with all visual processes after the formation of the retinal image (e.g., the retina/brain system). Now let us consider a patient before and after PRK surgery. The surgery does not affect the retina/brain system (N), so we can assume with good justification that any changes in the patient's CSF (C) will be caused only by changes in the OTF (O). Thus,

$$C_b(w) = [O_b(w)] \ [N(w)] \quad \text{and} \quad C_a(w) = [O_a(w)] \ [N(w)],$$

where the subscripts b and a refer to before and after surgery, respectively. We can then obtain

$$O_a(w) / \ O_b(w) = C_a(w) / \ C_b(w). \tag{4-3}$$

Thus, we can determine the change in the optical quality of a patient's eye (or of a population of eyes) (O_a / O_b) by measuring the ratio of CSFs before and after surgery (C_a / C_b). We have to be careful, however, to make the viewing conditions (e.g., lighting level, pupil size) comparable for the two measurements.

What types of change in the OTF (and therefore in the CSF) can occur with PRK? In terms of linear systems analysis, they fall into the categories illustrated in Figure 4-5: (1) changes that cause a high-frequency loss (such as refractive error), (2) changes that cause a mid-frequency loss (such as the spherical-like aberration that can occur due to the bifocal optics created by the corneal areas inside and outside of the ablation zone), and (3) changes that cause a loss across a wide range of frequencies (such as forward scatter which is also reported as a consequence of PRK). These three optical effects are discussed in detail in this chapter. Therefore, by using measurements of contrast sensitivity, we can assess the optical outcome of PRK (presuming we can find suitably comparable viewing conditions) and classify optical degradations into the three categories above.

Visual Performance Measures for Assessing the Impact of PRK

The visual performance measures in the existing PRK literature can be categorized in the following way: (1) optotype tests with high-contrast targets, (2) optotype tests with low-contrast targets, and (3) contrast sensitivity tests with gratings or letters. In addition, there are two very important factors in testing that should be clearly identified: (1) pupil diameter (because optical errors due to PRK might well appear at large diameters only) and (2) presence of glare source (because one possible outcome of PRK is the presence of glare intrusion).

High-Contrast Optotype Acuity Tests

High-contrast optotype tests present a variety of types of high-contrast targets that contain a range of spatial frequencies. Most PRK studies have amployed high contrast letter acuity tests. Ginsburg (1978) has argued that when a patient identifies letters at the 20/20 line, he or she is primarily using information in a band from ~10–30 cpd. Thus, it is difficult to determine what optical effect—high-frequency, mid-frequency, or uniform loss—has occurred when a patient's high-contrast optotype acuity is reduced. Furthermore, because the contrast sensitivity function declines very steeply at high spatial frequencies, the reduced contrast caused by optical scatter may not manifest itself at a measurable reduction in high contrast Visual Acuity.

Most clinicians regard the 20/20 criterion in optotype tests as the performance expected for well-corrected, healthy eyes. Actually, most young emmetropes, or well-corrected ametropes, will do better than 20/20, achieving 20/13 or even 20/10 performance. Thus, 20/20 is a rather lenient standard that can be met by subjects with compromised optics and vision.

It is frequently argued that optotype visual acuity tests are more useful clinically than contrast sensitivity tests. This argument is in general well justified because it has

been shown that optotype acuity tests are more sensitive than contrast sensitivity tests to anomalies in the retina/brain system and thus they are a better screening tool for the wide variety of clinical conditions faced by the practitioner. However, for the problem under consideration here—how to assess visual performance before and after PRK surgery—contrast sensitivity is the most appropriate measure because the retina/brain system is unaffected by the surgery. Some examples will help illustrate this point. Consider two subjects, one with normal optics and the other with significant spherical aberration. From Figure 4-5, one can see that optical transfer into the retinal image differs in these subjects, but mostly at medium spatial frequencies. A high-contrast letter acuity test determines the smallest letters that can be seen at high contrast, so performance on the test is determined mostly by optical transfer at high frequency. One might expect similar high contrast letter acuity in these two subjects even though one has compromised optics and the other does not. Contrast sensitivity measurements made at a number of different spatial frequencies, on the other hand, would reveal the mid-frequency loss in the aberrated eye.

Low-Contrast Optotype Acuity Tests

Low-contrast optotype tests present the same types of targets, but at lower contrast. By Ginsburg's (1978) analysis, patient performance on such tests manifests the use of information in a spatial-frequency band lower than 10–30 cpd. Verdon et al. (1996) have argued persuasively that such tests are likely to be more sensitive to uniform loss (e.g., glare) than are high-contrast optotype tests. Again, however, performance on low-contrast optotype tests by itself does not allow a clean determination of whether the optical loss is high frequency, mid-frequency, or uniform. Comparison of performance on high- and low-contrast optotype tests can allow such a determination.

Contrast Sensitivity

Contrast sensitivity tests that measure the complete CSF allow a direct determination of whether a reduction in optical quality is due to high-frequency, mid-frequency, or uniform loss. Specifically, if the compromise in optical quality is a high-frequency loss, then contrast sensitivity should be more affected at high frequencies (e.g., 20–40 cpd) than at medium frequencies (e.g., 3–6 cpd). If the compromise is a uniform loss, then contrast sensitivity should be affected in both spatial-frequency bands.

The Vistech VCTS charts are a popular tool for contrast sensitivity testing. They use printed gratings. There are nine circular patches in a series of decreasing contrasts at each of 5 spatial frequencies. The patient must identify the orientation of the grating before going to the next lower contrast level. Because so few contrast levels are available and because there is only one grating at each combination of spatial frequency and contrast, the contrast thresholds obtained are coarse. More-sensitive tests can be created using modern computer technology.

Letter contrast sensitivity as measured by the Pelli-Robson chart (Pelli et al., 1988) is a compromise between optotype acuity and contrast sensitivity testing, but because the letters in this test present a wide band of spatial frequencies to the patient, it also does not provide as clean an assessment of the type of optical degradation as does measurement of the CSF.

Pupil Diameter

Any test should include a measurement of the pupil diameter. Under dim lighting conditions, the pupil dilates and, consequently, the retinal image becomes subject to aberrations due to peripheral parts of the cornea. As already noted in this volume, there is clear evidence that post-PRK optics can involve aberrations off of the central cornea. Thus, one may find excellent contrast sensitivity in a post-PRK patient under bright lighting conditions only to find sub-normal sensitivity under dim lighting. The assessment of performance with respect to the tasks the patient is expected to conduct in the military should, therefore, include a determination of the likely pupil diameter in those tasks.

Disability Glare

For reasons described earlier in this chapter, it is also very important to include performance assessments in the presence of a glare source. The Brightness Acuity Tester (BAT) is a hand-held device that provides an internally illuminated hemisphere. The patient holds the device in front and views the test targets (e.g., optotypes or gratings) through a central aperture. The BAT provides a valid and reliable measure of disability glare when used with an appropriate acuity or contrast test (Elliot and Bullimore, 1993).

Performance Findings in PRK

General Assessments

Many studies report good to excellent visual outcomes after PRK. The most common means of assessment has been high-contrast optotype visual acuity tests such as the various versions of the high-contrast letter acuity test (e.g., Snellen, LogMAR, Landolt C, etc.). Frequently, no details are provided on the method of visual assessment or on the viewing conditions under which the assessment was conducted. In these cases, it is very likely that the assessment was made using a standard high-contrast letter acuity chart at photopic luminances with natural pupils and at the standard viewing distance used in the clinic. For reasons described in our theoretical analysis above, "visual function cannot be judged accurately and completely by traditional visual acuity charts" (Niesen et al., 1997, p. 139).

Uncorrected Visual Function

The precision of outcome (i.e., as far as achieving emmetropia) has been found to be related to the degree of preoperative myopia (Rao, 1996), the size of the ablation zone (Rao, 1996), and the amount of time postoperative. Issues concerned with the period of recovery will be important for military concern (and are addressed in Chapter 3), but the following discussions focus on longer-term results (greater than 6 months, typically 12 months or longer) that can be considered to be more productive of future function.

The usefulness of PRK in the military will be different than its usefulness in the civilian population. Moreover, the standards used to determine whether or not an outcome is acceptable should vary depending on the operating environments under which the soldier is expected to perform. Regardless of operating environments, if we work from the premise that the main purpose of PRK for military personnel is to eliminate the need for correction, then one standard would have to be post-PRK

uncorrected visual acuity (UCVA). For reasons stated in the theoretical analysis above, the best measure of uncorrected visual performance would be contrast sensitivity, but few such measurements have appeared in the literature. Thus, for now we consider the literature based on the use of the more common optotype acuity test. If high-contrast UCVA at mid-photopic lighting levels of at least 20/40 is acceptable, then the majority of studies show good outcomes, particularly if preoperative myopia is   -6.0 diopters. If high-contrast UCVA of at least 20/20 is acceptable, then the percentages of success decrease. Many sources, some providing details of the assessment method (Schallhorn et al., 1995, Shah and Hersh, 1996) and some not (Gimbel, 1993; Epstein, 1994), have reported good letter acuity outcomes. For example, Gimbel (1993), using 4.5- and 5-mm ablation zones, reported an average of 70 percent achieving 20/20 UCVA or better and 94 percent achieving 20/40 or better. Although Schallhorn et al. (1995) reported that 100 percent (30 eyes) achieved 20/20 using a 6-mm zone and the 4-m Early Treatment Diabetic Retinopathy self-illuminated (ETDRS) eye chart, Shah and Hersh (1996) found 62 percent achieving at least 20/20 and 100 percent at least 20/40 using a 6-mm zone and Early Treatment Diabetic Retinopathy chart with controlled lighting. Thus, high-contrast, photopic visual acuity shows reasonable outcomes, especially when the standard for uncorrected acuity is 20/40, but outcome success varies from study to study.

For reasons stated above in the theoretical analysis, there is good reason to measure performance at low contrast. A few studies have indeed assessed low-contrast optotype acuity (Lohmann et al., 1993; Butuner, 1994; Verdon et al., 1996; Niesen et al., 1997). Most of them reported best-corrected acuity rather than uncorrected. Of the ones reporting best-corrected acuity, all but one (Lohmann et al., 1993) reported losses in low-contrast visual acuity at 12 months postoperative. Even when the high-contrast optotype acuity is good, patients can complain of disturbed night vision (Kim, 1993; Dutt, 1994). Such reports, which probably reflect disability glare, should be followed up because they could be extremely important for assessment of PRK for particular military tasks such as night vision and use of visual imaging devices such as night vision goggles. In addition, a small number of studies have measured visual function under low illumination (where pupil diameter is large) and low contrast (where vision is more likely to be affected when the optical loss is uniform across a range of spatial frequencies). Lohmann et al. (1991) also examined the psychophysical effects of forward scatter on best corrected visual acuity (BCVA) without a secondary glare source. They find that high-contrast letter acuity is virtually unaffected, but the effects on vision become more pronounced as contrast is reduced. Low-contrast (5 percent) letter acuity was decreased by a factor of 3 immediately after ablation, and then returned to normal at 3–4 months, but showed a further decrease (factor of 2) between 6 and 12 months. Verdon et al. (1996) and Butuner (1994) used the Pelli-Robson letter contrast sensitivity chart; such measures are useful, but for reasons stated above, not as useful in our analysis as measures of complete contrast sensitivity functions. We could find only one researcher that measured the CSF: Corbett (1996 a and 1996b) found at 1-month postoperative, best-corrected sensitivity was reduced at high spatial frequencies, but at 12-months postoperative contrast sensitivity was reduced at all spatial frequencies with the most significant effect at medium spatial frequencies. This suggests that these PRK patients experienced a high-frequency loss initially, followed by a uniform loss as described above. This is an important result that should be replicated and understood better.

Using a "stray-light" meter that provides a direct measure of forward scatter, Lohmann et al. (1993) were able to show that the increase in forward scatter could be very significant at 3 months but largely resolved at 12 months. They also ran the same experiments on myopes with glasses, hard contact lenses, and soft contact lenses and showed that soft contact lenses were almost as bad as PRK at 3 months.

Studies examining the outcomes of PRK as a function of the degree of preoperative myopia indicate the importance of this variable in predicting success. For example, Rao (1996) found that 94 percent achieve UCVA of 20/40 or better with low preoperative myopia (e.g., a mean of 4.6±0.91), whereas only 72 and 28 percent achieved 20/40 or better in their moderate (-7.83±1.05) and high (-13.09±2.46) preoperative myopia groups. Seiler and Wollensak (1993) used four different preoperative myopia groupings: low (<-3.0 diopters), middle (-3.1 to –6.0 diopters), higher (–6.1 to –9.0 diopters), and high (>-9.1 diopters). They reported that 81, 49, 18, and 8 of patients achieved at least 20/20 and 99, 97, 60, and 41 percent achieved at least 20/40 in their low through high groups, respectively. The evidence indicates that consideration as a PRK candidate should be assessed relative to the candidate's degree of preoperative myopia in conjunction with the task and environmental work requirements.

Best-Corrected Visual Function

As discussed above, the best assessment of the success of PRK for military purposes will be whether or not uncorrected contrast sensitivity at medium to high spatial frequencies is sufficient to eliminate corrective lenses; this assessment should be made for a range of pupil diameters (manipulated by luminance level) that are suitable for the task requirements and with and without glare sources as appropriate for the task requirements. In the event that correction is still required, will there be any loss of best-corrected visual function? Although continuing to require correction after PRK would seem to defeat the purpose of using this procedure with military personnel, information about post-PRK best-corrected visual function will provide information about the percentage of PRK individuals who might not be able to perform their specified task even with additional correction.

Of the studies that provide few assessment details, many indicate post-PRK BCVA outcomes comparable to UCVA outcomes. However, some studies report losses in BCVA as well as other problems. Again, it is assumed that studies without details used high-contrast letter acuity charts under photopic illumination.

Using a 5-mm zone, Kim (1993) found that 95 percent of 135 eyes (preoperative, < -7.0 diopters) achieved at least 20/20 and 100 percent at least 20/40 after 1 year. Again using a 5-mm zone, Kim (1994) reported that 89 percent of 45 eyes achieved at least 20/25 at 2 years. In another study, Kim (1995) reported that all 35 eyes that were evaluated achieved 20/25 or better at 3 years. Using both 5-mm and 6-mm zones, Kalski et al. (1996) found that all patients achieved 20/20 at 6 months.

Lohmann et al. (1993), using a 4-mm zone, found comparable low- and high-contrast BCVA between their ten eyes and glasses-corrected controls. Dutt (1994) reported 100 percent of their 47 eyes achieved at least 20/20 even under medium glare (BAT).

Even with testing at high-contrast and photopic illumination, some studies indicate poorer outcomes. Ficker (1993) reported that 15 percent of 81 eyes lost at least 1 line BCVA after 1 year. When Corbett (1996) compared 5-mm (n=21) and 6-mm (n=19) zones with low preoperative myopes (< -4.0 diopters), 33 percent lost 1 line and 10 percent 2 lines in the 5-mm group, whereas 26 percent lost 1 line and none lost 2 lines in the 6-mm group. Almanzar et al. (Almanzar et al., 1996) compared multizone ablation versus a tapered transition zone with 20 moderate myopes (mean -8.30 diopters, range -7 to -11.75 diopters) who received each method in one eye. Of the multizone eyes, 37.5 percent lost 1 line BCVA. Twenty-five percent of the tapered transition zone eyes lost 1 line and 25 percent lost 2 lines BCVA.

Using a 4-mm zone, Gartry et al. (1992b) found that 82 percent of 120 eyes achieved an increase in BCVA over preoperative levels. However, 15 percent lost up to 1

line BCVA. Using 4.5–5.0-mm zones, Butuner (1994) compared their PRK patients (n=34) to age-matched controls and found significant reductions in 25 percent of PRK eyes in both high- and low-contrast BCVA compared with normal eyes. They suggest that Snellen acuity may be inadequate in assessing visual function post-PRK. Verdon (1996) using a 5-mm zone with 18 eyes found high-contrast BCVA reduced 0.5 lines and low-contrast BCVA reduced 1.5 lines. They also found greater losses with dilation and a glare source. Using a 6-mm zone, Shah and Hersh (1996) reported that that 24 percent of 45 eyes lost 1 line. Niesen et al. (1997), using a 5-mm zone, found that 25.8 percent of their 46 eyes lost 1 line and 10.8 percent lost 2 lines BCVA. Postoperative BCVA under low contrast was lower for all test conditions.

As with UCVA, with or without details of assessment, the literature consistently indicates that BCVA decreases with increasing preoperative myopia (Kim, 1993; Taylor, 1996; Corbett, 1996c; Rao, 1996). For example, the percentage of patients achieving 20/20 dropped from 95 percent for the low preoperative myopia group (-4.19±1.17) to 81 percent for the high group (-8.94±1.86) in Kim (1993) study, although 100 percent still obtained 20/40. Compared with their low preoperative group's results noted above, the results from the moderate group from Corbett (1996c) (mean -6.64 diopters) indicated that 55 percent lost   1 line and 15 percent   2 lines in the 5-mm group, and 33 percent lost   1 line and none lost 2 lines in the 6-mm group. Rao (1996) found that 2.9, 5.6, and 21.9 percent of their low (-4.60±0.91, n=35), moderate (-7.83±1.05, n=72), and high (-13.09±2.46, n=32) myopic groups lost   2 lines BCVA.

UCVA and BCVA Summary and Conclusions

It is very important to emphasize that 20/20 is not perfect vision and most individuals have considerably better VA (20/20 can be considered the lower boundary between normal and subnormal vision).   Thus, defining the percentage of eyes that achieve 20/20 is not the same as stating that this percentage achieves normal vision.

There is a growing consensus that preoperative myopia is a good predictor of postoperative BCVA and UCVA. Although we believe that high-contrast letter acuity is not the best means for assessing visual outcome, there is a large database using such tests, that we reviewed. The number of military individuals that will be acceptable candidates for surgery will depend on the range of acceptable UCVA (e.g., 20/20 versus 20/40) related to the individual's work environment. The fact that many studies find good UCVA after PRK may be a good indicator. Although BCVA results show greater variability compared with UCVA results, the fact that a number of studies find losses in BCVA under high-contrast, photopic illumination may be a serious concern. When one considers the varied and complex work environments military personnel are likely to encounter (e.g., low lighting, low-contrast moving displays, and/or observers), it may become necessary to develop and use more precise and task-appropriate assessment methods. For example, Kim (1994 p.233) noted that "visual quality decreased in 21.7 percent of patients two years after PRK. Thus, we usually do not recommend PRK to those whose profession depends on good visual quality (e.g., p.50 surgeons, draftspersons, taxi drivers, pilots)." Similarly, O'Brart (1994c) suggest, "Professional drivers and patients who regularly drive at night, especially on motorways and roads without lighting, should be made fully aware of the potential night vision problems after PRK." Thus, not only might there be reservations about using PRK for military personnel in terms of achieving good UCVA outcomes, but there are also concerns related to vision quality after PRK (e.g., haze, halos, reduced night vision) that will need to be taken into account.

Night Vision

Because many military operations are performed at night, night vision becomes an issue of special importance. Four fundamental changes occur when switching from day to night:

1. The pupil dilates from 3–4 mm up to 6–8 mm. Pupil dilation is larger for younger adults and virtually absent for the very old, and dilation will vary between individuals.

2. The neural machinery used for daylight vision changes from foveal and peripheral cones to (a) mainly peripheral rods with some cone function when artificial light sources are present, or (b) peripheral rods only when natural lighting (star, moon, sky) is present at night.

3. The signal-to-noise ratio in the visual stimulus decreases because of photon noise. This makes targets more difficult to see.

4. The night environment is often populated with light sources that are much brighter than the ambient illumination level. With the exception of the sun, such variations in illumination level are not present in the daytime environment.

Finding 13: The change in pupil size and the changes in the visual stimulus can have significant interactions with the optical effects of PRK. Large pupils will include the edge of the ablated zone. The edge of the ablated zone includes (1) increased haze (according to one study) and (2) a huge dioptric step (equal to the step between post-PRK Rx and pre-PRK Rx) that creates a bifocal visual system with decreased image quality and noticeable annular blur rings (halos) around bright light sources.

Reduced signal-to-noise ratio reduces visual contrast sensitivity (and resolution), and thus any additional reductions in contrast sensitivity may have added impact at night where more targets are already close to contrast threshold.

Although there are almost no studies of night vision after PRK, certain parallels can be made between low light level vision with high-contrast targets and low-contrast vision at high light levels. In both cases, the stimulus contrast has reduced the signal to noise ratio, visual acuity is reduced, and any reductions in contrast sensitivity due to poor optics will render more stimuli invisible.   There have been several studies of low-contrast acuity (e.g., Verdon et al., and Lohmann et al., 1991) that all show a similar trend: PRK has a bigger effect on low-contrast visual acuity than on high-contrast acuity. It is reasonable to conclude, therefore, that PRK will have a larger effect on vision at low light levels than on vision at high levels even without the increased pupil effects described above.

Finding 14: In combining the two effects (pupil dilation and the accompanying reduction in image quality) with the inherently larger impact PRK will have on low-light vision, it is reasonable to expect that the impacts of PRK on vision will be maximal at night.

Finding 15:   The presence of bright light sources in the nocturnal environment will have an additional detrimental effect on any eye with a scatter source such as the subepithelial losses of transparency present in all eyes during the 1–3-month postoperative period after PRK. Any older driver will confirm that small losses of transparency that go unnoticed during the day can make night driving very difficult because of oncoming and reflected headlights. The explanation is simple: The optics of all eyes have some scatter, and typically scatter has an angular selectivity (e.g., varying with the square of the angle) that scatters most of the light to areas of the retina near to the geometrical image location. Because the amount of scatter is usually quite small, the scattered light simply reduces contrast of objects near the source. In a daytime environment where adjacent objects have similar intensities, this small reduction in contrast is not noticed. However, at night when artificial light sources are

present that can be thousands of times more intense than the surrounding objects, one very bright light is enough to reduce the contrast of surrounding images to the point where they become hard to identify or even invisible. Therefore, the disability glare (forward scatter) experienced by some PRK eyes will be particularly detrimental at night.

The halos caused by the bifocal nature of the post-PRK cornea will be most visible at night because a bright halo will be seen around a bright light source. Also, because of pupil dilation, the intensity of the halo will increase at night. The intensity of the halo will also be larger when the ablation zone is smaller. For example, the halo will have 36 percent of the light within the central image for a 7-mm pupil and a 6-mm ablation zone, but there will be three times as much light in the halo when an 8-mm pupil and a 4-mm ablation zone are combined. Because these halos will be more intense at night, they will have the biggest impact on night vision. The only way to reduce this impact is to increase the size of the ablation zone.

The above analysis stems directly from the optical summary in an earlier section of this chapter. We now examine the experimental literature on night vision in PRK.

There are few night vision studies in the experimental and clinical literature, probably because there are no "standardized" night vision tests available to clinical research teams. Several studies used questionnaires to evaluate the level of problems with night vision, and some specifically asked about night driving. For example, Halliday (1995) reported that more than 60 percent of PRK patients experienced glare problems some of the time (presumably at night) at 1-year postoperative. O'Brart (1994b) reported that night vision problems were present in 45 percent of patients, but only severe enough to prevent safe night driving in 11 percent at 3-months postoperative; these percentages dropped to 38 percent and 5 percent, respectively, at 1 year postoperative. Hamberg-Nystrom (1995) reported that night vision problems were present permanently in 40 percent (sometimes 70 percent) of PRK patients. A similar number reported halos. O'Brart (1994c) reported halos in 45 percent of patients with 5-mm ablation zones (compared with 78 percent in Gartry, 1991 with 4-mm ablation zones), and both studies report about 10 percent having significant night vision problems. In the Gartry, study (4-mm ablation zone), these reports were taken after one eye had had PRK, and 10 percent reported that the night vision would be significantly compromised if the second eye was treated. In the one study that tried to remedy the night vision problems by prescribing a mild miotic (Alster, 1996), the night vision problems were improved by pupil constriction. Unfortunately, reducing pupil size at night reduces the visibility of all visual targets because a smaller pupil allows less light to reach the retina.

Finding 16: One study (Kriegerowski, et al., 1996) reported large reductions in low- contrast acuity in the presence of glare, problems with halos (100 percent post-PRK surgery, and 45 percent at 1 year), increased glare sensitivity that was still present in 66 percent at 1 year, and 19 of 26 patients would have failed the German night driving test based on these results and thus would not be licensed to drive at night in Germany. It is worth noting that studies of night driving (Anderson and Holliday, 1995) point out that high-contrast visual acuity measurements taken at high light levels overestimate visual performance under night driving conditions.

Finding 17: Given the military needs for optimal night performance, and the paucity of data (one ARVO abstract) on night vision with PRK, an obvious gap in the experimental literature exists. There is an immediate need for experimental studies of night vision after PRK.

Vision with Imaging Devices

There are some obvious mechanical advantages of PRK compared with glass lenses when using imaging systems that are close to the eye. For example, many imaging and goggle systems cannot be used with glasses, and if the PRK is successful in correcting refractive errors, then the soldier who previously could not use a goggle system or mask could now use it.

Finding 18: Imaging systems such as image intensification devices (e.g., night vision goggles) pose a special problem for PRK. These devices are designed to multiply the photons from a nighttime scene. In doing so they amplify an inherently noisy signal (reducing the light level is equivalent to reducing the signal-to-noise ratio because of the Poisson nature of photon distributions) and the amplification process adds its own noise. This reduced signal-to-noise ratio is compounded when the object has a low-contrast target (such as a sand dune in the desert) because a low-contrast object also has a low signal to noise ratio. These three factors (low light level, image intensification, and low contrast) already render some objects invisible that we might expect to see because of the high mean intensity of the night vision goggles. Any additional reduction in the signal-to-noise ratio in these marginal conditions could render even more stimuli invisible. It is therefore possible that a PRK procedure that allows high-contrast objects viewed in daylight to be seen with ease may render many low-contrast objects invisible when viewed with night vision goggles. The cause of the additional reduction in image contrast will result from increased scatter and aberrations caused by the procedure. Both of these optical effects spread to very low spatial frequencies and therefore will affect the image contrast of relatively large objects (e.g., sand dunes).

Finding 19: There is a desperate need for good psychophysical data on the effects of PRK on night vision with and without amplification.

An extremely important goal in the military is to allow our personnel to operate more proficiently than opposing personnel in extreme environments. In terms of visual function, there are numerous aspects to this goal. For example, it would be a clear advantage to be able detect and identify visual targets at a greater distance or at lower light levels than the opposition can. Visual demands, however, vary tremendously from one military situation to another, so it seems that no single measure of visual function will allow a meaningful prediction of task performance in the variety of military situations an individual might encounter.

As mentioned above, the most common test of visual function is the high-contrast letter acuity test. There is clear evidence, however, that letter acuity does not predict the ability to perform a variety of everyday tasks. One piece of evidence comes from the driving literature; there is essentially no correlation between driving ability (as measured by accident history and performance on road course driving tests) and letter acuity (Owsley and Sloane, 1987; Brabyn et al., 1994). Another piece of evidence comes from the aviation literature in which again there is essentially no correlation between letter acuity and measures of flying performance (Kruk et al., 1981; Regan et al., 1993). Yet another piece comes from studies of mobility which show that rather large reductions in acuity have little effect on the ability to navigate and walk through everyday environments (Pelli, 1986; Elliot, et al., 1996). We suspect that the same low correlation between letter acuity and task performance would be observed in a variety of military situations, such as flying at low altitude while using night vision goggles. Thus, we strongly recommend that other measures of visual function be used in assessing the suitability of PRK for the military and that those measures be tailored to the specific military task in question.

Summary of Post-PRK Visual Function and Recommendations for Future Research

Although the ultimate assessment devices must be designed and administered with specific military tasks in mind, we have some general observations and recommendations concerning the best avenues for such a research effort.

1. There are a limited number of optical degradations that can occur with PRK. They are summarized in terms of information transfer from the outside world into the retinal image in Figure 4-5. The fact that only a limited set of effects can occur simplifies the task of assessing post-PRK performance in military settings. There are two ways to create these optical degradations for performance research. First, one could simply test individuals who have had PRK and compare their performance which individuals who have not had the surgery. Second, one could simulate the various optical degradations by, for example, constructing contact lenses with properties that reproduce the degradations that could occur in PRK.   We believe that the second strategy is advantageous, at least in the beginning. The accuracy of the optical simulation should be tested by using the linear systems approach outlined earlier in this report. The ratio of CSFs in an individual, before and after PRK surgery, is a measure of the change in optical transfer. The ratio of CSFs in an individual with and without the simulated optical degradation would be the same if the optical changes due to PRK were simulated properly.   Work with simulated optical changes should, of course, eventually be followed up with tests of performance before and after PRK.

2. Some aspects of the viewing situation are particularly important to measure and examine in the research effort. These include the luminance, contrast, and spatial-frequency content of the targets; the subject's pupil diameter; and the position and intensity of glare sources.

3. When the research effort proceeds to an examination of PRK subjects, some aspects of the their history are particularly important to examine. These include the refractive error before surgery, the type of equipment used in the surgery, and the time since surgery.

4. In any research design, there should be a no-treatment control group. It seems clear that performance in most tasks will improve over time simply because the subject has more task-specific experience. A no-treatment control group (i.e., a group of individuals who do not receive the surgery, but are tested in the same fashion as those who do) allows one to measure this practice effect and factor it out in the analysis of the treatment effect per se.

5. The most daunting, yet most critical task, in assessing the consequences of PRK for military operations is the design and implementation of appropriate performance tests. We note that many critical military operations are conducted under extreme conditions in which the visual system's ability to pick up the required information is pressed to a variety of limits. For example, the use of night vision goggles in low-altitude flying at night reduces the signal-to-noise ratio presented to the eye; this is equivalent to the effect of reducing the retinal-image contrast. If a pilot were trying to detect or identify a target that was just visible with night vision goggles, the presence of an additional contrast loss due to PRK might render the target invisible.   We recommend, therefore, that performance tests be designed and conducted that require subjects to perform representative tasks under visual conditions that mimic those in the specific military situations concerned. It would be best to conduct such tests using with-subject designs so that the same subjects can be tested in the same tasks with different simulated optical degradations.   The more important results should ultimately be confirmed with PRK subjects and controls .

VISUALLY DEPENDENT SKILLS

The visual performance literature is rather sparse, but good data do exist on reading, face recognition, ambulation, driving, sports performance, and flying. We examine the impact of optical degradation on each of these activities. It is important to understand before reading this section that most of these studies describe the effect of reduced vision on relatively easy tasks performed at high light levels with easy to see targets. Because of this, it would be incorrect to interpret the resistance to visual degradation reported here as evidence that highly skilled military tasks performed under poor visibility conditions will also be resistant to visual degradation.

Sports Vision

There is a widely held view that most skilled sporting performance is highly dependent on good vision. Unfortunately, the experimental literature in this field is seriously lacking in both theory and data. For example, it is alarming to realize that one of the most significant publications in this field was a junior high school science project .(Applegate and Applegate, 1992). Add to this the marketing hype of "sports vision" and "sports vision training," and it becomes difficult to identify the actual visual requirements for most sports.

The concept that vision is critical to sporting performance seems unquestioned. The scarcity of young myopes and the preponderance of young emmetropes and hyperopes in sports seems to confirm this. However, when careful experimental studies are attempted, it is often difficult to identify any specific role for high retinal image quality.

Although some epidemiological studies indicate that athletes have slightly better visual skills than non-athletes (Coffey and Reichow, 1989), experimental studies fail to confirm that high-quality vision is critical for skilled athletic performance. For example, in an experimental study of golf putting accuracy (Aksamit and Husak, 1983), blindfolding the putter had no impact on accuracy. Not surprisingly, this result was contradicted in 1984 by a second study (Wannebo and Reeve, 1984). In an unpublished study at Indiana University (Bradley, 1990), no measurable effect on putting accuracy was observed by blurring the vision of the putter from 20/15 to 20/100.

In a study titled "The relationship between basketball shooting accuracy performance and certain visual attributes" (Beals, et al., 1971), a correlation was reported between visual acuity and basketball performance. This correlation was shown, on statistical grounds, to be spurious in 1973 (Dippner, 1973). More recently, an experimental study of the effect of blurring lenses on basketball shooting accuracy (Applegate and Applegate, 1992) found almost no impact of reducing visual acuity down to about 20/200.

At this time, therefore, it is not possible to make any strong conclusions about the impact of small (or even large) reductions in retinal image quality on sports performance. However, there is some experimental evidence to suggest that a small reduction in retinal image quality due to blur will have almost no impact on the performance of clearly visual tasks in sports. There is some basic vision research that supports this assertion.

Many skilled sporting activities involve alignment tasks (ball with hoop, racket with ball, and possibly target with a sighting device). It is worth noting, therefore, that alignment tasks in which the two objects to be aligned are spatially separated appear quite resistant to reductions in image quality.(Williams, et al., 1984)

Mobility Skills

Personal mobility is one of the most important factors determining quality of life. In our culture, two forms of personal mobility dominate: walking and driving. Both are highly visual skills, but the specific visual requirements of each skill are not well understood. Four general approaches have been taken to identify the role of vision in mobility:

1. experimental studies of normal individuals with simulated vision problems,
2. experimental studies of individuals with specific vision problems such a macular disease and cataracts,
3. correlation between visual performance and perceived mobility problems, and
4. correlation between visual performance and accident statistics.

Because PRK will introduce a reduction contrast or blur to what, in most cases, will be an otherwise normal visual system, the simulation studies on normals are perhaps most valuable for estimating the possible impact of PRK on mobility.

Walking

A detailed study of the visual requirements of walking by Pelli (1986) examined the effects of blur and reduced retinal image contrast on normal individuals. The results indicate that visually normal subjects were able to navigate around a course and navigate around a shopping mall without making large numbers of errors (bumping into obstacles, stopping, reversing) while their vision was *severely compromised*. Significant mobility errors occurred only when contrast was reduced to 2 or 4 percent of the normal. Errors also began to occur when the retinal image was blurred to reduce visual acuity to 20/2000. From this study, there is no indication that a small reduction in contrast or an introduction of a small amount of blur would produce any reduction in visual-guided mobility in an environment full of high-contrast objects.

A more recent mobility study with simulated cataracts (Elliot et al., 1996) observed that the reduction in contrast (0.65 log units) introduced by the simulated cataract had no effect on mobility under daylight conditions, but it did introduce significant mobility problems under nighttime illumination conditions. Subjects took longer to negotiate a course and they made more errors while traveling the course.

In an experimental study of patients with retinal disease, Marron and Bailey (1982) report that visually guided mobility performance was correlated to their contrast sensitivity deficits, but not to their visual acuity. However, in a study of cataract patients that did not measure contrast sensitivity, (Bernth-Petersen, 1981), patient reports demonstrate a correlation between visual acuity and visually guided mobility. Also, in a study of patients after cataract removal, Mangione et al.(1994) report a correlation between improved visual acuity and improved perceived mobility.

In summary, these studies are seemingly contradictory. Simulations indicate that visual acuity and contrast sensitivity can be reduced significantly without impairing mobility, but studies of patients with retinal disease and/or cataracts suggest that mobility is related to both contrast sensitivity (Marron and Bailey 1982) and visual acuity (Bernth-Petersen, 1981; Mangione, et al., 1994) A couple of points are worth mentioning here. First, the correlation observed by Marron and Bailey (1982) was for patients with severely reduced macular contrast sensitivity. Therefore, these data would be in agreement with the observations of Elliot et al. (Elliot, 1996) who found that reductions in contrast sensitivity under nocturnal conditions did have an impact because nocturnal conditions will produce large reductions in normal contrast sensitivity analogous to those produced by pathology. These studies produced similar results

because, in the Marron (1982) study, it is the disease that reduced all of the subjects' CSFs, and in the Elliot et al. (1996) study all of the subjects' CSFs were reduced by the low light levels. The Bernth-Petersen (1981) and Mangione et al. (1994) studies used questionnaires, and the connection between decreased mobility and vision may reflect the time patients spend in poor lighting conditions (e.g., reading, walking, and driving at night).

Therefore, it appears that a consistent story is developing. Reductions in image contrast or introductions of blur will have no measurable effect on daytime walking and mobility, but they may have some effect on *nocturnal* mobility. For example, the subjects in the study by Elliot et al. (1996) all had 20/20 acuity while viewing through the contrast attenuator at high light levels, but they still had mobility problems at night.

Driving

Using an elderly group (60–74 years) of normal drivers with 20/20 acuity, Wood and Troutbeck (1995) used a simulated cataract to evaluate daytime driving performance on a controlled traffic-free course. Their cataract simulation introduced about a 1.0 log unit reduction in contrast sensitivity which introduced significant changes in driving performance. Drivers were much slower (45 percent increase in time to navigate a course) and made significant errors in positioning the car on the road.

In light of the results from the mobility studies, it is important to point out that these driving experiments were carried out under daytime conditions, and that the simulated cataract had a very significant effect on retinal image contrast (a reduction by a factor of 10). Because the PRK will reduce retinal image contrast by much less, we might expect a much smaller or perhaps a zero impact on daytime driving under good visibility. However, this is pure speculation without the data to back it up. It is also important to emphasize that the subjects used in this study were much older than the expected PRK candidate.

A recent report by Higgins et al. (1996) simulated reduced visual capability using simple defocus. They found that some driving skills are unaltered when visual acuity is reduced to 20/200 (legal blindness), whereas other driving skills were affected. We expect to find that very small amounts of blur (e.g., 0.25 diopters) will have no measurable effect on driving skill, but this is pure speculation at this time.

The Special Case of Night Driving

Difficulty with night driving is one of the classic problems faced by many having a wide range of visual problems. Classic examples are middle-aged and older patients who have early nuclear sclerosis of the crystalline lens and who suffer difficulties with night driving. Theory predicts that increased intraocular scatter in older eyes is the cause of the night driving problems. A small fraction of scattered light in the eye would typically have no effect on vision because it would cause only a small reduction in contrast. However, while driving at night it is not unusual for drivers to be viewing a poorly lit road. The road may have a luminance of less than 1 cd/ m², but on the road there may be a truck with headlights of a luminance close to 1-million cd/ m². Even if 0.1 percent of the 1-million cd/m² headlight is scattered onto the adjacent area of the retina that is imaging the road ahead, contrast of the road features will be reduced by approximately 3 log units (1/1,000). Because contrast sensitivity is never higher than 1,000 (threshold never lower than 1/1,000), this means that all road features will have their contrast reduced to less than 1/1,000 and hence will become invisible. This "visual disability glare" effect is experienced by all drivers to some extent, but in older drivers it becomes exaggerated so that night driving can become hazardous, and many people

modify their driving behavior to avoid night driving. Our optical analysis predicts similar problems with PRK patients, particularly during the early period of healing in which the cornea has haze.

Flying

Although few people are actively involved in flying, most Americans are passengers at some time in a commercial jet. It is then of critical importance to understand the ramifications that PRK may have on flying. To qualify for US Air Force flight training, candidates must have 20/20 unaided visual acuity. This criterion assumes that good visual acuity and hence good retinal image quality are essential for piloting.

We were only able to identify a few studies that provide any insight into the visual requirements of flying. Kruk et al. (1981) found that contrast thresholds were not a good predictor of pilot performance on an aircraft landing simulator. However, Ginsburg et al. (1983) showed that contrast sensitivity was critical in detecting oncoming aircraft. However, more recent studies by the US Air Force contradicted Ginsburg's conclusions (Task and Pinkus, 1987; O'Neal and Miller, 1988), indicating no correlation between contrast sensitivity and flying skills.

Face Recognition

Arguments have been made that it is the low spatial frequencies (large features) within a face that are important for recognition, (Ginsburg, 1980) whereas others have pointed out that high spatial frequencies (fine detail) are important (Fiorentini, et al., 1983), and still others have argued that the middle spatial frequencies are important (Owsley and Sloane, 1987). One group showed a correlation between face recognition and contrast sensitivity, whereas a recent paper found a high correlation between face recognition acuity and word-reading acuity.(Bullimore et al., 1991). That is, if the face is far away (and hence small), the ability to recognize the face will be correlated with visual acuity.

Unfortunately, these studies do not provide any great insight into the relationship between the magnitude of vision loss and the ability to recognize a face. However, with ocular pathology that reduced letter acuity by about 0.5 log units, face recognition (and word recognition) dropped by 1.0 log unit, indicating that face recognition acuity will be affected more than letter acuity.

Reading

Reading is perhaps one of the most obvious everyday tasks that requires excellent vision and a high-quality optical image in the eye. Unfortunately, the experimental literature is only just beginning to come to grips with the visual demands of reading.

One of the most significant studies of reading in normal individuals has documented that reading is only contrast dependent close to threshold levels (Charman and Saunders, 1990; Legge, et al., 1987). They found that as long as letter contrast was significantly suprathreshold, reading speed and letter contrast were almost independent. However, if letter contrast approached threshold, reading speed fell precipitously. Therefore, since most text is printed with high-contrast ink, and most reading has letters much larger than 20/20 characters, we might expect that most reading will be unaffected by PRK.

However, adverse reading conditions, such as low luminance or small, low-contrast letters, may approach threshold. Disease or environmental effects such as fog may yield the same result. In these cases, even a small contrast reduction or blur may have a significant effect on reading performance. (Collins et al., 1989; Bullimore and Jacobs, 1993).

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Appendix A

Acronyms and Abbreviations

AIBS - American Institute of Biological Sciences
BAT - Brightness Acuity Tester
BCVA - best-corrected visual acuity
BSCVA - best spectacle-corrected visual acuity
bFGF - basic fibroblast growth factor
BrdU - bromo deoxyuridine
CSF - contrast sensitivity function
DoD - U.S. Department of Defense
DTAF - dichlorotriazinyl aminofluorescein
dUTP - deoxyuridine triphosphate
FDA - Food and Drug Administration
GSH - gluathione
GSSH - glutathione oxidized
HGF - hepatocyte growth factor
IF - Interferon
IL - Interleukin
IOP - Intraocular Pressure
KGF - keratinocyte growth factor
LASIK - laser assisted *in situ* keratomileusis
MMP - Matrix Metalloprotein
OTF - optical transfer function
PARK (or PRKa) - photorefractive astigmatism keratectomy
PDGF-BB - platelet derived growth factor
PERK - Prospective Evaluation of Radial Keratotomy
PMN - polymorphonuclear leukocyte
PRK - photorefractive keratectomy
PTK - phototherapeutic keratoplasty
RK - radial keratotomy
SEAL - sea, air, and land (specially trained member of the Navy)
  SMA - alpha smooth muscle actin
SPARC - secreted protein, acidic, and rich in cystein
SPARS - Scientific Peer Advisory and Review Services
TGF- 1 - transforming growth factor
TUNEL - transferase with dUTP-biotin nick-end labeling
TNF - tumor necrosis factor
UCVA - uncorrected visual acuity
USAMRMC - U.S. Army Medical Research and Materiel Command
UV - ultraviolet

Appendix B

Terms of Reference

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                    TERMS OF REFERENCE
                          for
                     AIBS PEER REVIEW
                          of
           PHOTOREFRACTIVE KERATECTOMY (PRK) RESEARCH
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I. Purpose

To conduct detailed, independent peer review of the available research on
the surgical procedure known as PRK. The review will:

        (1) evaluate the scientific and clinical data relating to PRK
(primarily of the last 5 years),

        (2) from this evaluation, assess the near- and long-term outcomes of
PRK, and

        (3) relate this information to visual performance specific to
military tasks and in conditions likely to be encountered in military
operations and/or with unique military equipment.

This review is requested by the U.S. Special Operations Command (USSOCOM),
the U.S. Army Medical Research and Materiel Command (USAMRMC), and the
U.S. Navy Medical Research and Development Command (USNMRDC).

An independent AIBS review panel will be formed to conduct the review,
meeting at least twice, once to provide panel members with military
background and issues, and then to conduct a conference of the panelists.

A report of the findings of the review panel will be submitted to the
USAMRMC within 30 days following the review meeting.

II. Review Responsibilities

The review panel will be specifically charged to:

        1. Evaluate the existing scientific and clinical data, with
individual committee members surveying the literature from the perspective
of their particular disciplines, and using these criteria:

                a. scientific merit of the research and/or quality of the
case observations,

                b. comparability of subject population to the military
population, and

                c. relevance of outcome measures to military requirements.

2. Assess the procedures, intended outcomes, secondary effects, and unintended consequences of PRK. Particular emphasis should be given to these specific concerns:

    a. Brief summary of PRK.

        1) Equipment and procedures currently approved for use in the U.S.

        2) Relevant government regulations, professional association standards, and voluntary guidelines.

    b. Candidacy for PRK surgery.

        1) Range of needed correction for which PRK is likely to be useful (in terms of military performance).

        2) Medical conditions that preclude use of PRK.

    c. Visual outcomes.

        1) Expected results after PRK, including visual performance outcomes such as acuity, contrast sensitivity, and night vision (include characterization of the relative merits of devices and procedures used to assess various aspects of visual performance).

        2) Comparison of typical PRK outcome to best corrected vision with spectacles or contacts for personnel who normally require vision correction (please comment on the visual performance tradeoff between PRK and spectacle-corrected vision).

        3) Comparison of typical PRK outcome to visual performance of individuals requiring correction without their correction (e.g., lost or broken spectacles, or habitual nonuse).

        4) Effect of PRK surgery on visual performance with imaging devices and displays (e.g., night vision goggles, heads-up displays, diving masks, and protective devices (such as laser protective spectacles and chemical protective masks).

    d. Duration of benefit.

        1) How long does the benefit last?

        2) What factors influence the duration of benefit?

        3) What effect does PRK in young adults have on the visual changes that normally occur after age 40?

        4) Are there additional risks associated with a second PRK?

e. Potential adverse effects.

1) Severity and frequency of adverse effects such as halo, haze, glare, scarring, infection, pain, and changes in tearing.

2) Susceptibility of the eye to injury, illness or infection.

3) Factors influencing the outcomes, including age, degree and type of correction needed, gander, race, or any other characteristic.

4) Problems related to pressure changes which which might be encountered in military operations such as in aviation, mountaineering, underwater diving, and parachuting.

f. Differences in equipment and procedures used for PRK.

1) Procedural differences which may affect the outcome.

2) Differences in preoperative treatments that affect the outcome.

3) Differences in postoperative treatments that affect the outcome.

g. Any other issues that nay be relevant to PRK use in military personnel.

h. Comment on any of the above issues as relevant to more recent related procedures including specifically LASIK.

3. From the above evaluations and determinations, make explicit and focussed recommendations for any research still needed to address these concerns.

III. Selection of Peer Review Panel

Independent reviewers will be selected, organized into a review panel, and managed by AIBS through a panel chairperson. The panel chairperson and panel members will be chosen by AIBS following AIBS guidelines. Proposed membership and their vitae will be submitted to the COR for comment on potential conflict of interest and scientific credentials in advance of the first panel meeting. Criteria for selecting teen members are:

1. Competence. The primary criterion for selecting scientists for membership on a peer team is recognized competence

in a principal science discipline to be covered by the team. Such
competence is generally determined by a record of steady publication of
research results in the recognized, peer-reviewed scientific journals.
Strong endorsement by several science peers, in conjunction with the
publication record, strengthens the degree of competency.

2. Previous Experience. A second criterion is previous experience
on peer evaluations Such experience usually denotes broad knowledge of a
scientific field, specific knowledge in a subdiscipline of the field and
the ability to work cooperatively in a group. The reviewers should have a
collective knowledge in the following subjects, in order of importance:

a. research optometry

b. corneal physiology

c. evaluation of visual performance

d. clinical experience in ophthalmology

3. Experience as Military Advisor. A third criterion, although not
critical, is previous experience on a peer review panel judging the merit
of military supported scientific research. Most reviewers are
knowledgeable of NIH or NSF research programs, but experience on a panel
for military provides the reviewer with knowledge of unique military needs
and requirements. Previous experience as a consultant to the military can
also be a plus.

4. Conflict of Interest. Currant DOD members will not be
considered for candidacy, nor will individuals with PRK industry conflicts
of interest. Reviewers will be requested to sign a statement such as:

"I certify that I am not aware of any matter that might reduce my
ability to serve in the review of the DOD PRK Research Assessment in
an objective and unbiased manner or that might place me in a
position of conflict, real or apparent, between my reviewer
responsibilities and other interests."

IV. Management of Peer Review Panel

1. To implement the general review process, a panel of experts will be
formed, with a single chairperson and nine additional members. A number of
steps will be followed to assure uniformity of the review procedure. The
panel will meet with the supporting staff from AIBS prior to the meeting to
discuss the review process. The panel chairperson will explain the mission

statement and the charge to the panel, review the meeting format, the report format, and the study time table and make writing assignments.

2. The panel chairman will be in charge of the panel meeting and is responsible for the conduct of the meeting, including setting discussion time limts, soliciting comments from observers as needed, and insuring that each segment of the research area receives thorough and fair evaluation. The deliberations of the panel may be recorded (taped) by AIBS to assist in the preparation of the program evaluation report. The AIBS staff member acting as executive secretary for the panel will assist the chairperson and panel members with developing the review panel report.

3. The two review meetings will last one to three days. If possible, the panel will produce a rough draft of its report that summarizes the panel findings, evaluations and recommendations prior to their departure from the second review. After the second review meeting, AIBS will circulate a formatted second draft to the panel members for their editing and then produce a final draft from the edited copy.

4. The panel report will include:

    a. Introduction and charge to the panels

    b. Executive summary and combined recommendations

    c. Summary evaluation of the research area

        1) evaluations of literature within specific research areas

        2) recommendations for each research area

    e. Appendices

        1) panel listing

        2) fiat of attendees

        3) agenda

5. The AIBS staff will prepare the final copy of the study report for signature of the steering committee chairman and AIBS project director and submit the report to the USAMRMC The AIBS will provide fifty (50) bound copies of the report.

6. The points-of-contact listed below will provide AIBS with copies of documents to be reviewed that are not readily available through open sources. A listing of open source

documents to be considered will be provided, AIBS will retrieve and disseminate these reports to panel members as necessary. The points-of-contact will each briefly address the panel in the first meeting to outline conditions, environments, and requirements which are unique to the military and contextually relevant to the panel and their charge. The POC will also answer any further questions concerning the objectives of the review.

      7. All arrangements for the AIBS including lodging arrangements, travel and per diem, transmittal of read-ahead documents and other meeting related material is the responsibility of AIBS.

V. Budget

These terms of requirements will be included in a modification of the scope of work of the currant AIBS Contract No. DAMD17-97-C-7005; CS: Ms. Patricia Nelson; COR LTC Karl Friedl.

VI. Time and Location

      Meeting date: To be determined, but starting not later than 30 September 1997

      Meeting location: AIBS facility, Reston, Virginia

VII. Points of Contact

USAMRMC coordinator: LTC Richard Levine, (301) 619-7301

USSOCOM coordinator: LTC John Leu, (813) 828-5442

USNMRDC coordinator: CAPT(s) Dennis McBride, (301) 295-0878

Appendix C

List of Meetings and Meeting Participants

First Meeting: October 21-22, 1997, American Institute of Biological Sciences (AIBS) Offices, Sterling, Virginia

Panel Members and Staff:

Howard P. Cupples, M.D.
Martin S. Banks, Ph.D.
Arthur Bradley, Ph.D.
James M. Brown, Ph.D.
H. Dwight Cavanagh, M.D., Ph.D.
James V. Jester, Ph.D.

Winston W. Kao, Ph.D.
Peter S. Reinach, Ph.D.
Sally S. Twining, Ph.D.
J. Richard Keefe, Ph.D.
Noel E. Eldridge, M.S.

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Second Meeting: December 18-19, 1997, AIBS Offices, Sterling, Virginia

Panel Members and Staff:

Howard P. Cupples, M.D.
Martin S. Banks, Ph.D.
G. Richard Bennett, O.D.
Arthur Bradley, Ph.D.
James M. Brown, Ph.D.
H. Dwight Cavanagh, M.D., Ph.D.
James V. Jester, Ph.D.

Winston W. Kao, Ph.D.
Peter S. Reinach, Ph.D.
John E. Sutphin, M.D.
Sally S. Twining, Ph.D.
J. Richard Keefe, Ph.D.
Noel E. Eldridge, M.S.

Briefers and Invited Participants:

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